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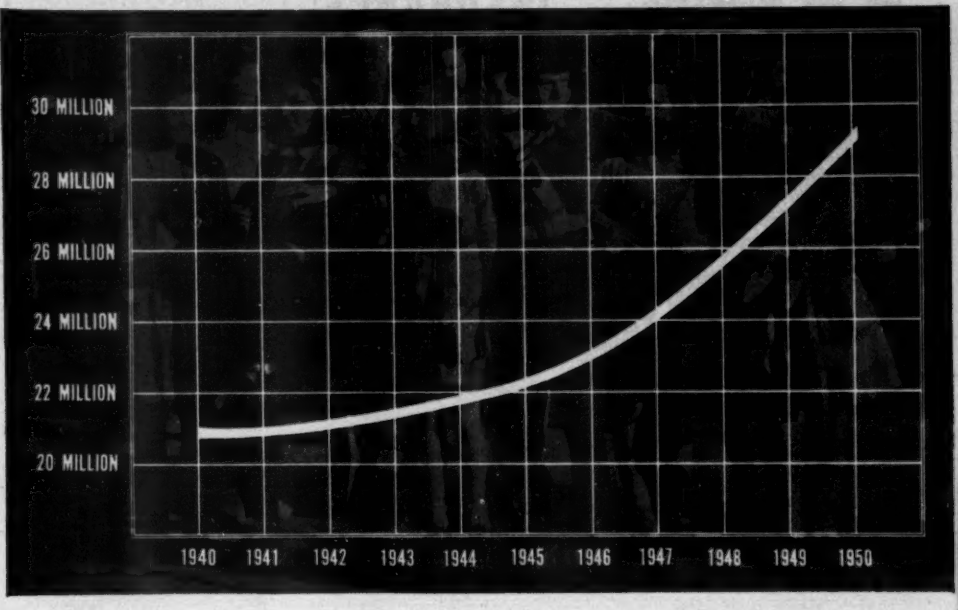

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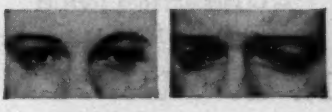
Some young eyes can take it  . . . some eyes cannot!

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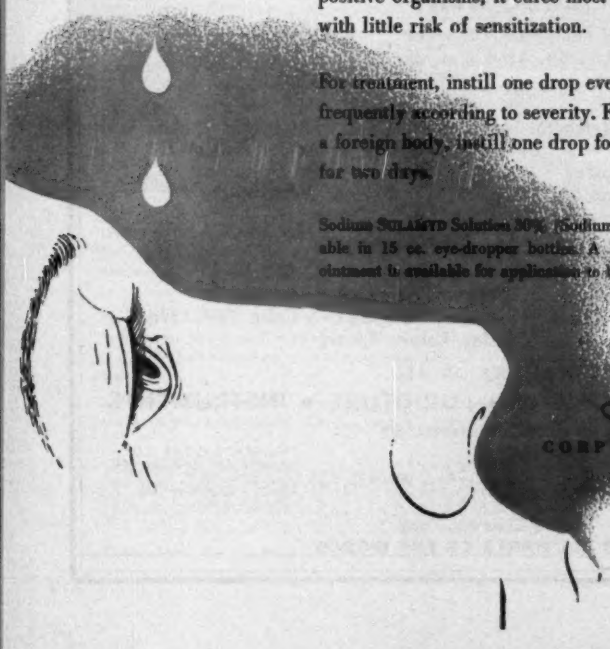

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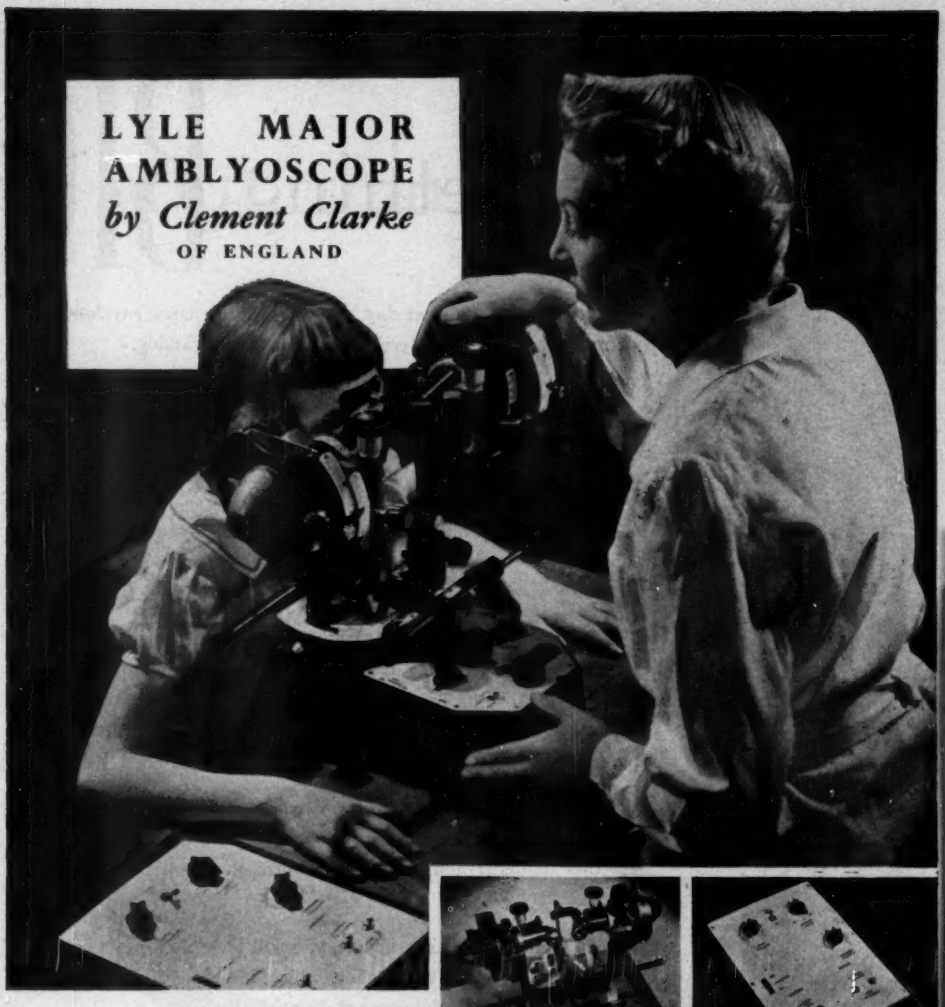

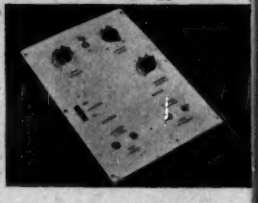

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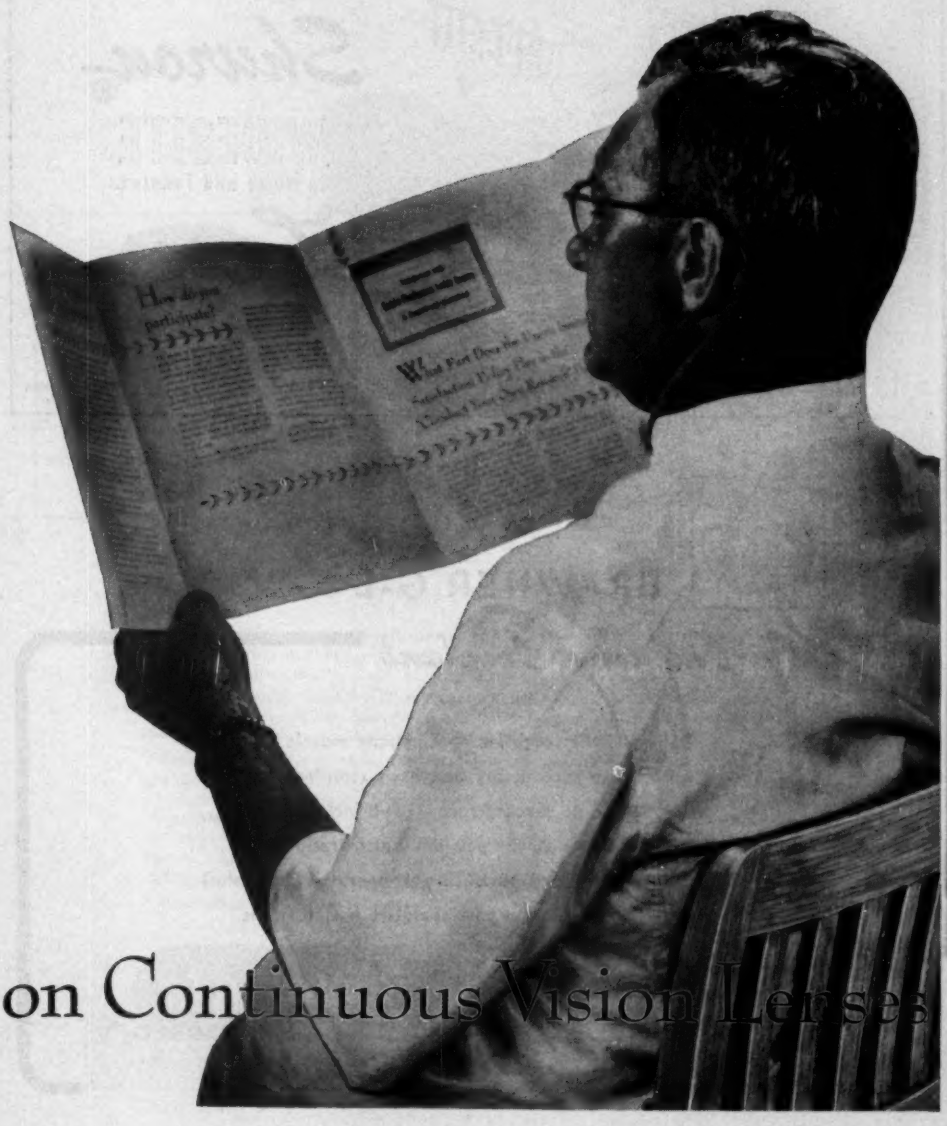

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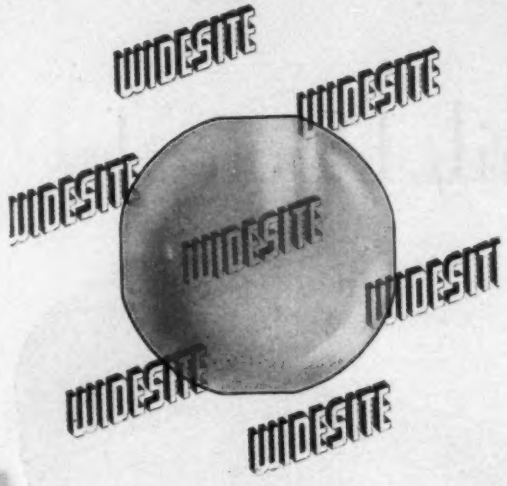

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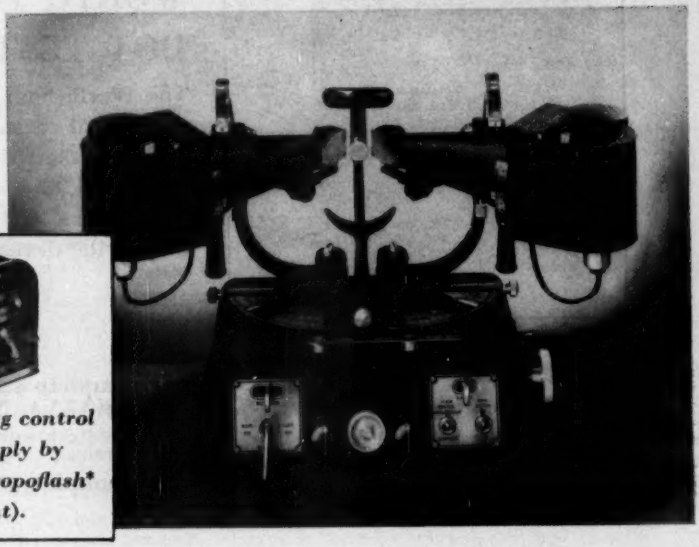

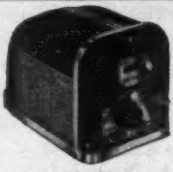

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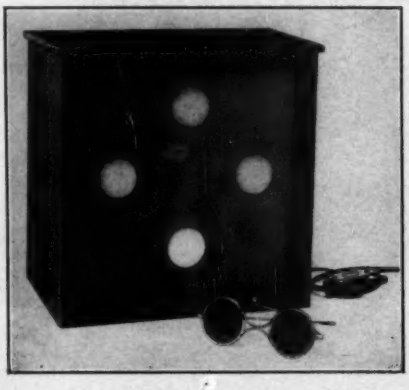

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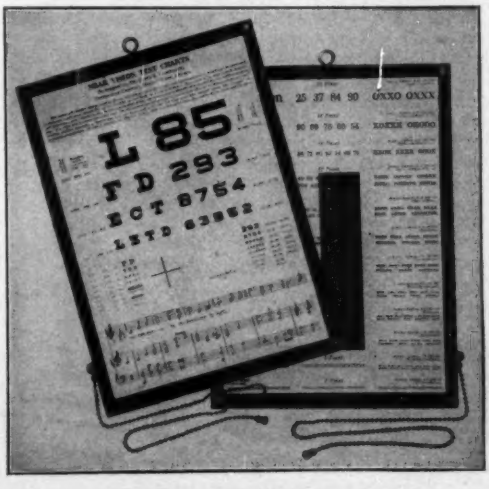

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CLINICAL MEASUREMENTS OF AQUEOUS OUTFLOW

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IT IS THE purpose of this paper to report certain observations on facility of outflow and rate of formation of aqueous humor in human beings. Special consideration will be given to those changes which are concerned in the pathogenesis of glaucoma. The basis for this report is provided by measurements made on patients' eyes by means of a tonographic method, already published.[1] Approximately 1,000 of these measurements have been made on 600 clinically examined eyes, a majority of which were glaucomatous.

This study makes available a quantitative method of evaluating glaucoma. Specifically, it enables one to evaluate the respective roles of resistance to outflow and rate of formation of aqueous humor. This possibility has apparently not previously been explored in the manner of the present study. Previous investigations of aqueous outflow have yielded information only in terms which have left it undetermined whether the changes which were detected in outflow resistance represented a major or a minor influence in producing variations in the intraocular pressure in glaucoma. Thus, the literature contains many unresolved conjectures as to whether various sorts of glaucoma might be due to obstruction of outflow or to hyperformation of aqueous humor, or to both.

METHOD

The method by which resolution of this uncertainty has been sought in the present study is as follows: The amount of resistance to, or, inversely, the facility of, escape of aqueous from the eye has been determined by allowing an electronic Schiøtz tonometer to rest for four to five minutes on a patient's topically anesthetized cornea, an initial increase in the intraocular pressure caused by the weight of the tonometer being followed by a slow fall toward the original pressure as the aqueous is expressed from the eye at a greater than original rate. The whole performance of the eye during the four to five minutes under these conditions is recorded automatically from the electronic tonometer on a moving-paper electrocardiograph strip in terms of the amount of indentation of the eye by the tonometer. The data obtained in this manner are then converted into terms of actual intraocular pressure, increment of intraocular pressure due to the weight of the tonometer, and change in ocular volume. The rate of change in these factors with time permits calculation of the rate of expression of aqueous due to the artificially increased pressure. The relation between these last terms, i. e., the relation of pressure to rate of aqueous loss, defines physically and quantitatively one of the factors, the facility of aqueous outflow, which govern the steady-state intraocular pressure. For convenience,

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1. Grant, W. M.: Tonographic Method for Measuring the Facility and Rate of Aqueous Flow in Human Eyes, Arch. Ophth. **44**:204-214 (Aug.) 1950.

this facility of aqueous outflow is expressed as a coefficient in units of cubic millimeters per minute per millimeter of pressure (Hg). The third factor, the rate of aqueous formation, in the relation of intraocular pressure, facility of aqueous outflow, and rate of aqueous formation is calculated from the first two measured quantities. It is considered that the rate of outflow is a simple function of the pressure and that if C cu. mm. of aqueous is found to escape per minute per millimeter of pressure and the intraocular pressure is P mm. in the steady state, the net rate of flow of aqueous, or the equivalent rate of formation, is $(P - 4)$ times C cu. mm. per minute.[2]

However, it is to be noted that determination of the facility of aqueous outflow and of the net rate of flow by the tonographic method is predicated on the existence of an essentially steady state, i. e., equal rates of formation and outflow and constant intraocular pressure, before the measuring procedure is applied. If the intraocular pressure is changing before the measurement is begun, an error is introduced which is a function of the rate of spontaneous change of intraocular pressure. The error is considerably worse for the value of net rate of flow than for the facility of outflow.

The calibration data which have been employed in the conversion of the recorded data into terms of intraocular pressure are those which in 1950 Dr. Jonas S. Friedenwald regarded as his best and generously made available for the present investigation, although they had not been published. He has referred to this as his "absolute" calibration. The changes in ocular volume, similarly, have been calculated from his data, utilizing his equations and his constant in relating ocular volume and pressure in the presence of distortion by the Schiøtz tonometer.

The limitations of the method employed in this study appear to be determined primarily by the limits of accuracy of tonometric measurement and calibration. The uncertainties arise in some degree from purely instrumental problems of sensitivity and accuracy, but in larger degree from the problems of instrumental calibration in terms of pressure and volume change in a biologically variable structure such as the eye. Although the best available calibration data have been utilized, the physical and mathematical aspects of the application and extension of these data are extremely complex and fraught with a variety of uncertainties. Some reassurance of justification in the manner in which Friedenwald's data have been employed has been obtained from the preliminary results of an independent experimental evaluation, in which measurements on enucleated human eyes have indicated reasonable conformity of calculated and experimentally determined values for pressure and volume. Whether there may be some moderate absolute error affecting equally the values for facility of aqueous outflow and those for rate of aqueous formation is not of serious import in the present clinical investigation, since the interpretations which are made here are based primarily on comparison of values for different types of eyes rather than on absolute values. Unfortunately, both absolute and comparative values from patient to patient may be affected by variations in the coefficient of scleral rigidity among the population. This factor can be measured and corrected for in the calculations, but in the present series of cases it has not always been feasible to evaluate the scleral rigidity adequately. Instead, in order to minimize the error from this source, conclusions have been based on measurements of a sufficiently large number of eyes to permit some

2. A simple proportionality between the intraocular pressure and the rate of escape of aqueous from the eye has been found to hold experimentally in human and rabbit eyes post mortem from a pressure of 50 mm. Hg down to approximately 4 mm. Hg, although the simplest physical relation which one might have expected, envisaging fixed escape channels, would have been a proportionality with the square root of the pressure. This experimentally determined deviation from the physical square-root law suggests, in conformity with Thomassen's observations on aqueous veins (Thomassen, T. L.: On the Exit of Aqueous Humor in Normal Eyes, Acta ophth. **28**:479-487, 1950), that in the eye an increasing number of channels for outflow open up with increasing pressure. It is unfortunate that the low-pressure limit at which aqueous outflow may cease in the living eye has not been directly determinable and that it has been necessary to use the value obtained in eyes post mortem. However, this factor is not a consideration in the determination of the facility of outflow. Only the absolute values for rate of formation would be influenced by a change in the value for the low limit, and, within reasonable margins of error, the principal conclusions of this paper would not be altered.

statistical validity despite the expected individual variations. An additional factor which must be considered in assessing the reliability of the values obtained by the tonographic method, and one which at present is rather difficult to evaluate fully, is the possibility that the measuring procedure itself might alter the very factors which it is intended to measure. From the evidence so far available it seems that this effect must ordinarily be small, although it may conceivably become significant in certain types of eyes. This potential source of error may presumably be minimized by employing the smallest possible weight.

Interference from excessive eye movement may occasionally vitiate a measurement and necessitate its discard. Transient circulatory variations may occasionally influence the intraocular pressure during tonography, but the evidence so far available indicates that tonographic determination of aqueous outflow does not fundamentally involve vascular phenomena. In general, any transient extraneous interference in tonographic measurement is detectable by inspection of the paper-strip recording. An estimate of the reliability can be obtained from the smoothness of the curve. In the event of small irregularities, improvement in reliability has been sought by prolonging the period of measurement.

Considering all the various limitations which have been listed, and the variability of results in individual normal eyes, it appears that only differences of more than 20% in values obtained for the coefficient of facility of aqueous outflow should be regarded as significant. In all cases in the present study, conclusions have been based on measured changes considerably greater than this. Individual differences in values for rate of aqueous formation are considered significant only if greater than approximately 40%. Future improvements in accuracy of calibration, formulation, and instrumentation will undoubtedly alter the present values numerically, but I believe that such changes will not be of a magnitude to affect the validity of conclusions based on the present data.

RESULTS

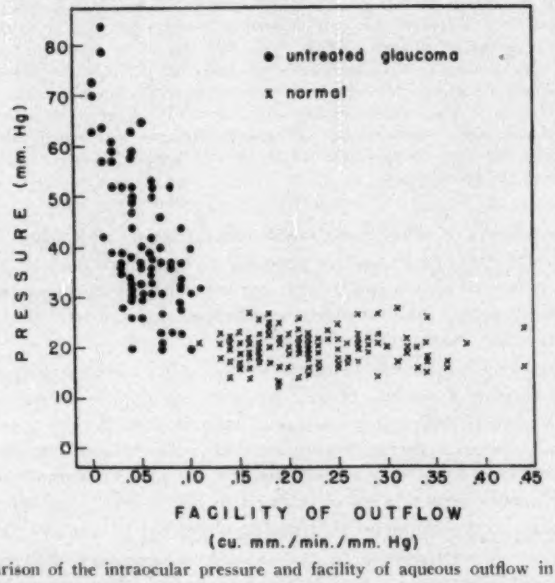
The 600 human eyes on which tonographic measurements were made have been divided into several clinically distinctive groups for characterization. Some of the eyes have been measured only a single time, but many have been measured at several stages of glaucomatous involvement or at different stages in treatment, and this has proved particularly informative.

Normal Eyes.—One hundred and eighteen normal eyes have now been measured, and an average facility of outflow of 0.22 cu. mm. per minute per millimeter of pressure has been found, with individual values ranging from 0.11 to 0.44 cu. mm. The distribution is shown in the accompanying chart. The normal net rate of flow, or rate of formation of aqueous, was estimated by the present method to average 2.4 cu. mm. per minute, with a range of from 1.1 to 5.3 cu. mm. Age has not been found to be a factor in determining either facility of outflow or rate of formation.

Aphakic Eyes.—A relatively slight, and possibly insignificant, difference from the normal is found in eyes which have had uncomplicated cataract extractions. In 10 well-healed aphakic eyes most of which had had intracapsular extractions with iridectomy, the average value for facility of aqueous outflow was 0.19 cu. mm. per minute per millimeter of pressure, as compared with 0.22 cu. mm. for normal eyes, and the average rate of aqueous formation was 2.0 cu. mm. per minute, as compared with a normal of 2.4 cu. mm. The range of variation of the individual values was similar to that of normal eyes.

A general comparison of normal eyes with untreated glaucomatous eyes may be of some interest before the findings in individual types of glaucoma are discussed. A suitable comparison can be made with the random collection of 75 eyes in the present series which had definite clinical diagnoses of glaucoma of all types but which were untreated at the time of measurement, except for a few eyes on which the measurements were made during a remission and which will be discussed subsequently. In

this heterogenous group of glaucomatous eyes the facility of aqueous outflow ranged from 0 to 0.11 cu. mm. per minute per millimeter of pressure, and the rate of formation, from practically 0 to 3.5 cu. mm. per minute, with an average of 1.5 cu. mm. per minute. By comparison of these values with the corresponding values for normal eyes, and by inspection of the chart, in which the relation of the intraocular pressure, expressed according to the standard clinical scale, and the facility of aqueous outflow is shown for both normal and untreated glaucomatous eyes, certain differences between these two groups are apparent. The glaucomatous eyes consistently have a poorer facility of aqueous outflow, i. e., a greater resistance to outflow, than the normal eyes, and the rate of formation of aqueous is not increased in the glaucomatous eyes, but, on the average, appears to be somewhat less than in the normal eye.[3] In all untreated glaucomatous eyes in this group, as well as in approxi-



Comparison of the intraocular pressure and facility of aqueous outflow in 118 normal eyes and 75 untreated glaucomatous eyes.

mately 150 additional glaucomatous eyes of various types, which are to be discussed subsequently, all elevations of the intraocular pressure were adequately accounted for by the degree of increase of resistance to aqueous outflow; and, contrary to popular belief, in no case was the glaucoma attributable to hyperformation of aqueous.

3. It may be further deduced that the increased resistance to outflow is of a frictional sort, and that glaucoma is not ordinarily produced by an antecedent elevation of pressure in the veins receiving the aqueous outflow, for, by the methods of measurement and calculation employed in this study, an elevation of the low-pressure limit for outflow in glaucomatous eyes would have caused the values obtained for rate of formation of aqueous to be higher, rather than somewhat lower, than normal.

The difference which has been observed between the facility of aqueous outflow of normal eyes and that of glaucomatous eyes suggests that evaluation by tonographic measurement may be of some significance in early diagnosis or in determination of predisposition to glaucoma. Preliminary results indicate this to be the case in primary wide-angle glaucoma, but a considerably longer period of observation will be necessary before a definite assessment of the prognostic value can be made. This is to be the subject of a future communication.

Narrow-Angle Glaucoma.—In the acute form, narrow-angle glaucoma provides a striking correlation of tonographic findings with other clinical observations, particularly the appearance of the angle of the anterior chamber with the gonioscope. In each of 10 eyes with acute narrow-angle glaucoma, with pressures ranging from 79 to 49 mm., marked obstruction to aqueous outflow was indicated by the very small values which were obtained for the facility of outflow—0.01 to 0.06 cu. mm. per minute per millimeter of pressure. This abnormal resistance to outflow was great enough in all instances to account for the whole rise in pressure without necessity of postulating any hyperformation of aqueous. In fact, the calculated rate of formation was uniformly somewhat low, ranging from 0.5 to 2.9 cu. mm. and averaging 1.8 cu. mm. per minute. In all of these eyes which it was possible to examine with the gonioscope the angle of the anterior chamber was seen to be closed by forward displacement of the periphery of the iris. These findings were entirely consistent with the concept that obstruction to aqueous outflow and the associated elevation of tension in acute narrow-angle glaucoma are due to blockage of the channels for aqueous outflow by the iris in the angle. Additional evidence for this mechanism was provided by measurements and observations which were made on 15 eyes during and after treatment for acute narrow-angle glaucoma. When the angle was caused to open up either by iridectomy or by use of miotics, as ascertained by gonioscopy, the facility of aqueous outflow returned to normal and the tension was normalized, except in those cases in which bands of peripheral anterior synechia had formed. In these instances, in which the disease was converted to a chronic form by formation of synechias, obstruction to aqueous outflow was found to persist somewhat in proportion to the synechial involvement of the angle. In a small number of eyes which had suffered an acute attack of narrow-angle glaucoma and had been successfully relieved by miotics, it was observed that the tension thereafter could remain normal for a period without further treatment, but these eyes were, of course, vulnerable to further attacks. During the period of such remission the angles appeared open, though very narrow, and the facility of aqueous outflow was found to be normal.

The companion eyes of those having acute narrow-angle glaucoma were observed in 13 instances to have extremely narrow, but open, angles, and in these eyes the facility of aqueous outflow and the intraocular pressure were normal. However, evidence that these companion eyes were also susceptible to development of acute glaucoma was obtained from observation of a subsequent change to obstructed outflow, with closed angle and high pressure in several instances. In one such instance measurements were made immediately before, during, and after an acute attack. Before the attack the facility of outflow and the tension were normal, but a few minutes later the tension began to rise rapidly and reached 70 mm. within 45 min. At this stage, although the pupil remained constantly at 3.5 to 4 mm. in diameter,

the iris was seen gonioscopically to be bulging forward in the periphery into contact with the back of the cornea, and the facility of aqueous outflow had become reduced markedly to approximately 0.02 cu. mm. per minute per millimeter of pressure. An hour after application of carbachol drops, when the pupil had become miotic, the facility of aqueous outflow returned again to a normal value of approximately 0.22 cu. mm. per minute per millimeter of pressure. The pressure was then essentially constant at 17 mm., and on gonioscopic examination the periphery of the iris was seen to have become separated from the cornea and trabeculum.

It appears that the occurrence of narrow-angle glaucoma is dependent on the physical apposition of the iris against the aqueous-outflow channels and that slight physical dissimilarities in companion eyes may influence their susceptibility to valve-like angle closure. The present study suggests that if an increase in rate of aqueous formation has anything to do with precipitating an attack by bulging the iris forward, it must be of brief duration, since no evidence of hyperformation has so far been obtained in this study from numerous measurements at various stages.

In the subacute and chronic forms of narrow-angle glaucoma the same sort of mechanism appears to exist, in that obstruction to aqueous outflow measured tonographically can be satisfactorily correlated with the tension and with the degree of closure of the angle. In the subacute and chronic forms the degree of obstruction to outflow was found to be moderate in comparison with that in acute narrow-angle glaucoma. Outflow appeared to be obstructed functionally and reversibly in some instances by forward bulging of the periphery of the iris, but in most eyes there was also some degree of permanent obstruction by peripheral synechias. In some eyes only by intensive use of miotics could the facility of aqueous outflow and the tension be improved to normal medically, but relief of the obstruction due to forward bulging of the iris was generally aided by iridectomy. After iridectomy the angle was seen to become wider, as it did in treatment of the acute form, and the outflow of aqueous was found to be facilitated to the extent permitted by residual peripheral anterior synechias.

It is of some interest that of 29 patients whose narrow-angle glaucoma had become chronic, the disease was found to be bilateral in 26, but that in 13 of 19 patients who were having their first attack or two of acute glaucoma the disease at that stage was essentially monolateral. The companion eyes, which were still clinically normal except for very narrow but open angles, consistently had normal facility of aqueous outflow and rate of aqueous formation.

Primary Wide-Angle Glaucoma.—The eye with this form of glaucoma was found to differ in several respects from the eye with narrow-angle glaucoma. In eyes with wide-angle glaucoma the iris was never seen to bulge forward to close the angle; in fact, in most instances the angle was indistinguishable gonioscopically from a normal angle. Nevertheless, all abnormal elevations of intraocular pressure were found to be completely accounted for by decreased facility of aqueous outflow. In general, the amount of resistance to outflow and the associated ocular tension varied in a less labile or erratic fashion in wide-angle than in narrow-angle glaucoma. From examination of eyes with primary wide-angle glaucoma in various stages of the disease, it appeared that an early feature of the disease was an appreciable decrease in the facility of outflow as compared with that of definitely normal eyes. In some of the eyes with subnormal facility of outflow which were examined at a

stage when the glaucoma was essentially latent, the ocular tension was not significantly elevated most of the time, presumably on account of a low rate of aqueous formation, but under close observation the tension was found on occasion to rise well into the 30's. In another group, it has been suspected that primary wide-angle glaucoma is developing because both the facility of aqueous outflow and the tension have become borderline between the definitely normal and the definitely abnormal. In a few of these eyes additional evidences of glaucoma have appeared to add weight to the suspicion, but longer observation will be necessary before the prognostic significance of borderline findings can be properly evaluated.

In the more overt stages of wide-angle glaucoma, in which the tension is chronically elevated and damage to the optic nerve may occur, the disease has been observed to be almost always bilateral. The bilaterality in occasional instances may not be evident by the ordinary means of clinical examination, but by tonographic measurement there can usually be found a facility of outflow in the companion of the glaucomatous eye which is poorer than that of definitely normal eyes, probably presaging later overt development of glaucoma. Wide-angle glaucoma was found in the present study to be bilateral by the usual clinical standards in 30 of 37 patients with the disease, and by the standards of tonographically measured facility of aqueous outflow in 35 of the 37 patients.

Among untreated eyes with primary wide-angle glaucoma, impairment of facility of outflow has been encountered in all gradations, from the lower limit of normal to a moderately severe degree of obstruction, corresponding in general to the tension level and the clinical severity of the disease, although the degree of damage of the optic nerve is less consistently related. The graded distribution of values for facility of outflow, from the lower limit of normal down, suggests that during the development of primary wide-angle glaucoma the transition from the normal to the abnormally obstructed state may be gradual. In untreated narrow-angle glaucoma, by contrast, values for facility of outflow show greater extremes of distribution and characteristically may vary rapidly from normal, in the phases in which the angle is open and the tension normal, to markedly reduced readings when the angle is closed and the tension elevated.

Glaucoma Capsulare.—In eyes in which the onset of glaucoma has apparently been associated with exfoliation of the lens capsule, particularly in eyes with angles of moderate width and no other evident cause for the glaucoma, it has been assumed that the diagnosis was glaucoma capsulare, although very little exfoliated material could be seen in the angle. Elevation of tension in these eyes, also, was found to be due only to increased resistance to aqueous outflow. This type of glaucoma was found to be monocular, with normal outflow present in the other eye much more commonly than was the case with primary wide-angle glaucoma (in 4 of 9 cases of glaucoma capsulare). Unfortunately, no tonographic observations have yet been made on the effects of lens extraction in eyes with glaucoma capsulare.

Secondary Glaucoma.—When glaucoma has occurred secondary to an intraocular inflammation, such as iridocyclitis, it has been shown by tonographic measurements at various stages in the disease that elevation of tension is associated with diminished facility of aqueous outflow, but that under certain conditions the tension may be found in the normal range despite considerable obstruction to the outflow

of aqueous. It has been observed that with mild signs of inflammation in the aqueous there may be moderately increased resistance to aqueous outflow with the tension elevated, but with the rate of formation still nearly normal. However, in association with an increase in flare and cells in the aqueous, the tension has been noted at times to become normal, or even subnormal, despite persisting obstruction to outflow, presumably by reason of a diminished rate or efficiency of formation of aqueous. It may be postulated that the secretory transport of ions into the posterior chamber decreases in efficiency the leakier the blood-aqueous barrier becomes. In general, in secondary glaucoma, in addition to the common factor of reduction of facility of aqueous outflow, a considerable variation in the rate of formation, but not hyperformation, appears to be characteristic. The reduction of facility of outflow tends to increase the intraocular pressure, while the impairment of formation tends to decrease it, the resultant effect on the pressure being determined by the degree to which one of these influences may outweigh the other. In secondary glaucoma the disturbance appears commonly to be a monocular condition, for of 18 cases, a bilateral abnormality of tonographic measurements was found in only five.

The evolution of secondary glaucoma has been observed to follow several different courses. In eight instances, uveitis with secondary glaucoma has been observed to improve rapidly, with a complete return of all tonographically measureable factors to normal. In more protracted forms of inflammatory disease, peripheral anterior synechias have formed, which subsequently have been associated in some cases with chronic glaucoma, due to persistent obstruction of aqueous outflow after the inflammatory phase of the disease had subsided. In cases of uveitis of marked chronicity extensive peripheral anterior synechias have been observed, correlated with much obstruction to aqueous outflow, but in some instances with the tension in the normal range for long periods, even after the inflammatory disease was quiescent. The depression of aqueous formation in these cases is presumably correlated with damage and atrophy of the ciliary body. However, it is noteworthy that, although severe chronic obstruction to outflow may be compensated by a low rate of formation, a critical situation may be obtained thereby in which small absolute changes in obstruction or formation may cause large changes in tension.

A relatively unusual kind of secondary glaucoma due to leakage from a hypermature lens has been studied in one instance before and after cataract extraction. Prior to operation, there was a considerable flare in the aqueous, and the facility of aqueous outflow was reduced to 0.03 cu. mm. per minute per millimeter of pressure, with the pressure elevated to 71 mm., but several weeks after operation, when the eye was clinically normal and aphakic, the facility of outflow and tension were found to have become normal.

Glaucomatocyclitic Crisis.—Observed at various stages in three cases, this unusual form of acute monocular wide-angle glaucoma was found to be characterized by considerable obstruction to aqueous outflow during an attack, without significant change in rate of formation and without closure or synechias of the angle. During periods of remission the facility of aqueous outflow was found to be normal, or at times even greater than in the companion eye, with some relative hypotony.

Glaucoma Associated with Anterior Synechias.—In this category have been included eyes in which glaucoma appears to be due to peripheral anterior synechias produced by an antecedent ocular disturbance which is no longer active. Among

the eyes which have been measured tonographically, the commonest disturbances productive of anterior synechias and glaucoma have been previous secondary glaucoma, postoperative and post-traumatic inflammatory reactions, protracted postoperative flat anterior chamber, and iris bombé or narrow-angle glaucoma in which pupillary block has not been relieved early enough by iridectomy. Included are most instances of so-called aphakic glaucoma and glaucoma following posterior dislocation of the lens when these conditions have become chronic.

In general, the degree of obstruction of aqueous outflow has been found by tonographic measurement to be roughly proportional to the extent of synechial obstruction of the angle estimated gonioscopically. Both the proportion of the angle involved and the density of the synechias, estimated by transillumination, appear to be correlated with the measured degree of obstruction of outflow. In cases in which the whole circumference has been sealed off by a dense synechial band, the facility of outflow has been measured as essentially zero and the tension has been in the 70's. In one instance, that of companion aphakic eyes, one of which was normal and the other had just half of the circumferential angle closed off by an iridocorneal adhesion, the value for facility of outflow was normal in the first eye, but only half as great in the second.

Elevation of intraocular pressure has been approximately commensurate with the measured degree of obstruction of outflow in some cases, but in a number in which there has previously been considerable intraocular inflammation the elevation of pressure has been disproportionately small. As already mentioned in connection with secondary glaucoma, it is assumed that in these cases the mechanism for formation of aqueous has been impaired.

Low-Tension Glaucoma.—A small number of observations have been made on a puzzling group of elderly patients who, despite normal ocular tensions, have typical glaucomatous cupping and atrophy of both optic nerve heads. The tonographic findings in this condition have been sufficiently diverse as to suggest at least two varieties of this condition. In several patients whose tensions have been reliably known for some years to have been normal, but who have had definitely progressive cupping and optic nerve atrophy, tonographic measurements have indicated the facility of aqueous outflow and rate of formation of aqueous to be entirely within the normal range. These circumstances suggest that in these cases the abnormality lies primarily in the optic nerves or their supporting structures. In several other patients, whose tensions have been known for a relatively short period and whose visual field changes may be more static, tonography has given definitely subnormal values for both the facility of outflow and the rate of formation of aqueous. It seems possible that these persons may have had overt, but unrecognized, glaucoma in the past and that their ciliary body may now have become atrophic. More prolonged observation will help in deciding.

Surgical Treatment of Glaucoma.—The effect of various surgical procedures on aqueous outflow in glaucoma has been studied by comparing the preoperative and the postoperative tonographic measurements. Iridectomy, either peripheral or complete, in the presence of narrow-angle glaucoma has produced improvement of the facility of aqueous outflow in proportion to the amount the angle of the anterior chamber has become opened. The limitation of improvement is approximately in

proportion to the persistence of peripheral anterior synechial obstruction of the so-called filtration area. The effect of iridectomy in primary wide-angle glaucoma has not been observed, but in a small number of normal cataractous eyes iridectomy combined with intracapsular lens extraction appears to have caused little change in the facility of aqueous outflow.

The so-called filtering operations, such as iridencleisis and trephination, have been found to increase the facility of aqueous outflow to normal or greater than normal when they are successful, or to leave the facility of aqueous outflow poor, or even to make it poorer than before operation, when they are unsuccessful. Trephination in general was found to produce the greatest increase in facility of outflow, not infrequently to values greater than normal, with some attendant hypotony. No decrease in rate of formation has been observed in association with marked lowering of the tension by trephination; in fact, when the tension has been lowered to 14 mm. or below there has usually been an increase in rate of formation to 2.5 cu. mm. per minute on the average, approximating the average rate in normal eyes. Effective control of tension by cyclodialysis has been found to be dependent primarily on improvement of the facility of aqueous outflow, but in practically all instances in which the tension has been reduced to 12 mm. or less in the absence of miotics a reduction in the rate of formation has been observed, to an average of 0.9 cu. mm. per minute. This low rate of formation, compared with the normal rate in trephined eyes at comparably low tensions, suggests that cyclodialysis may impair the formation of aqueous humor in some way, as well as improve the facility of outflow. Control of tension by cyclodialysis has been correlated in all instances with the establishment of a cleft between sclera and ciliary body, which is visible with the gonioscope. The effects of goniotomy, goniopuncture, and cyclodiathermy have not yet been examined.

Medical Treatment of Glaucoma.—Comparison of tonographic measurement in the presence and in the absence of the use of drugs permits an evaluation of their mode of action. However, because of the short duration of action of most drugs, the approximation of steady-state conditions may be poor. As previously noted, this circumstance reduces the accuracy of the tonographic method and requires special consideration in the evaluation of results. Accordingly, in the present study only those effects which have been observed with reasonable consistency have been accepted as dependably real. Comparisons have been made of comparable groups of glaucomatous eyes without treatment and other groups with treatment and also of conditions in individual eyes under various forms of treatment. The latter type of comparison seems to be the more informative.

The lowering of tension in glaucoma by locally applied miotics is found commonly to be accomplished by an improvement of the facility of aqueous outflow. In narrow-angle glaucoma the improvement in outflow appears to be correlated with opening of the angle, but in wide-angle glaucoma no significant change in the width of the angle has been observed despite measured improvement in outflow. In narrow-angle glaucoma of acute or subacute type, when the mechanical obstruction of the angle by the iris has not persisted long enough for the formation of synechias, relief of the attack by miotics has been observed to return the facility of outflow, tension, and rate of formation all to the normal range in six of six cases. On the other hand, in chronic narrow-angle glaucoma with peripheral anterior

synechias, although in six of seven cases an observed lowering of tension by miotics was wholly accounted for by the measured amount of improvement in facility of outflow, it was commonly found that the facility of aqueous outflow did not come up completely to the normal range, even when the tension was essentially normalized (nine out of 15 cases). It is inferred that in these eyes there may be a persistence of the somewhat subnormal rate of formation of aqueous, which was noted previously as a tendency in eyes with untreated glaucoma. In primary wide-angle glaucoma it was also observed that the amount of lowering of tension by miotics was usually adequately accounted for by the degree of improvement of aqueous outflow (11 of 15 eyes), but that even though normal tensions were obtained the facility of outflow commonly persisted somewhat below normal (19 of 31 eyes); again, this would be explainable on the basis of continued subnormal rate of formation. In glaucoma from anterior synechias secondary to an antecedent ocular disturbance, the response to miotics was essentially of the same nature, six out of eight cases having sufficient increase in facility of outflow to account for the amount of decrease in pressure. The amount of improvement in facility of outflow with miotics in some of these eyes has been surprising, in view of the apparent extent of synechial involvement of the angle. A twofold or threefold increase in facility of outflow has not been unusual, but only in two eyes has the outflow attained the normal range. In glaucoma capsulare, on the other hand, in only one case out of five was enough facilitation of outflow found for the observed lowering of pressure. The possibility of a depressant effect on formation is to be considered in this situation, but the total number of cases of glaucoma capsulare is statistically small. Evidence for a depression of aqueous formation by miotics was found in only 8 of the 36 eyes with wide-angle, narrow-angle, or synechial glaucoma which were measured with and without medication. The average value for rate of formation for 67 glaucomatous eyes under treatment with miotics, with the tension below 30 mm., was slightly less than that for 85 eyes with untreated glaucoma—1.34 cu. mm., as compared with 1.45 cu. mm., per minute. It seems that lowering of intraocular pressure by suppression of aqueous formation is a relatively uncommon mode of action for miotics. Further investigation is undoubtedly needed.

The effect of epinephrine in lowering intraocular pressure has been measured so far in only a few heterogeneous cases. Both in secondary glaucoma and in primary glaucoma in conjunction with sufficient miotic medication to keep the pupil small, the facility of outflow was improved commensurate with pressure decrease in five of six eyes.

SUMMARY AND CONCLUSIONS

Measurements have been made in a series of patients of the facility with which the aqueous humor can be expressed from the eye, utilizing a tonographic method employing an electronic tonometer and recording galvanometer. The rate of formation of aqueous in these eyes under steady-state conditions has been calculated from the steady-state pressure and the measured coefficient for facility of outflow. The net rate of outflow has been found experimentally to be a direct function of pressure from approximately 4 to 50 mm. (Hg) pressure.

In glaucomatous eyes elevation of tension above normal has been found in every instance to be due exclusively to abnormal resistance to aqueous outflow, and no case of glaucoma due to hyperformation of aqueous has been observed. In narrow-

angle glaucoma, the amount of obstruction to outflow by measurement and the degree of closure of the angle estimated by gonioscopic examination have been well correlated, as has the elevation of intraocular pressure. In primary wide-angle glaucoma, decreased facility of aqueous outflow was consistently found, although no closure or gonioscopically visible obstruction of the angle was present. In secondary glaucoma, measured obstruction to aqueous outflow was also responsible for the elevation of tension, but this form of glaucoma was peculiar in that spontaneous return to normal or low-pressure levels was the result in some cases of return of facility of outflow to normal, but in other cases it apparently was the result of a decrease in rate of formation of aqueous with abnormal resistance to outflow persisting. Surgical treatment in general was beneficial only when it improved the facility of aqueous outflow. Iridectomy, either peripheral or complete, in eyes with narrow-angle glaucoma improved outflow toward normal in proportion to the degree of opening of the angle obtained. Treatment with miotics was effective principally in improving the facility of aqueous outflow, but in a small proportion of cases there was indication of a depressant effect on aqueous formation.

It is concluded that the increase in intraocular pressure in glaucoma is practically always, possibly exclusively, caused by increased resistance to outflow of aqueous humor from the eye (i. e., subnormal facility of outflow), and not by hyperformation of the aqueous humor. The beneficial effect of current surgical and medical treatment is achieved principally through improving the facility of aqueous outflow.

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Miss Elizabeth O. Cushing has assisted in all aspects of this investigation, and Dr. Harry E. Braconier has cooperated in examination of some of his patients with cyclodialyses. Stimulation has been furnished by frequent discussion with Dr. Paul A. Chandler.

ABSTRACT OF DISCUSSION

Dr. Jonas S. Friedenwald: It has long been known that when the tonometer is allowed to rest on an eye for a protracted period the intraocular pressure tends to fall. This so-called massage effect has been studied by a number of authors. Thomassen and, especially, Kronfeld have shown that the massage effect is diminished in eyes with uncompensated glaucoma. Moses and Bruno attempted to place this analysis on a quantitative basis by relating the increasing volume of the corneal indentation during prolonged tonometry to the average excess of the intraocular pressure during tonometry over that present in the eye before the measurement was begun.

It has been Dr. Grant's great achievement to bring this type of measurement into the range of clinically significant procedures. He has accomplished this, on the one hand, by greatly refining the tonometric recording system, and, on the other, by taking account in his estimate of the volume of fluid expressed from the eye—not merely the increase in the volume of the tonometric indentation, but also the shrinkage, i. e., the diminished distention of the eyeball as a whole during the period of the falling intraocular pressure.

Dr. Grant has said that the validity of his estimates depends on the reliability of the data which I have made available to him out of the study on calibration of tonometers undertaken for the Committee on Standardization of Tonometers of the American Academy of Ophthalmology and Otolaryngology. These data have not yet been published in full, but I hope to be able to make them available in print in the near future. In view of the dependence of Dr. Grant's data on my previous measurements, it becomes my responsibility to analyze the sources of error and the

range of error in these data. This analysis implies no criticism of Dr. Grant's work. Most of the sources of error which I shall enumerate are thoroughly familiar to him. It is, in fact, a great satisfaction to me that the data which I have compiled, even in their present crude form, have been shown by Dr. Grant's significant clinical results to be sufficiently accurate for this type of application.

The first step in Dr. Grant's analysis is the estimate of the amount of fluid expressed from the eye during tonometry. The formula which he uses may be expressed in approximate form as

$$(1)\quad \Delta V = \frac{1}{K_T} \log \frac{P_{T1}}{P_{T2}} - V_2 + V_1$$

where ΔV is the volume of fluid expressed, P_{T1} and P_{T2} are the intraocular pressures with the tonometer resting on the eye at the beginning and the end of the measurement, and V_1 and V_2 are the volumes of the corneal indentation at the beginning and the end of the measurement. This formula is based on my finding that, to a reasonable approximation, the relation of pressure to volume in an eye when it is distended by intraocular injection of fluid can be represented by the empirical formula

$$(2)\quad \Delta V = \frac{1}{K_D} \log \frac{P_1}{P_2}$$

and when it is distorted by the tonometer, by

$$(3)\quad V = \frac{1}{K_T} \log \frac{P_T}{P_0}$$

where P_T is the pressure in the eye with the tonometer resting on it, P_0 the pressure before tonometry, and V the volume of the corneal indentation. Now, unfortunately for mathematical simplicity, K_D, the coefficient of rigidity with respect to ocular distention, and K_T, the coefficient of rigidity with respect to ocular distortion, are not necessarily equal. Dr. Grant's application of the tonometric distortion coefficient, K_T, to the situation during prolonged tonometry, when the eye changes in respect both to distention and to distortion, is an extrapolation of the empirical formula into a region where it does not necessarily apply accurately. A formula similar to Grant's, and free from this objection, can be derived as follows:

Considering the eye immediately before and immediately after prolonged tonometry, and representing the initial and final pressures by P_{O1} and P_{O2}, the fluid lost by ΔV, then, since we are dealing only with changes in distention,

$$(4)\quad \Delta V = \frac{1}{K_D} \log \frac{P_{O1}}{P_{O2}}.$$

On the other hand, when the tonometer is first placed on the eye we are dealing only with distortion. Therefore

$$(5)\quad V_1 = \frac{1}{K_T} \log \frac{P_{T1}}{P_{O1}}.$$

Similarly, when the tonometer is finally removed from the eye

$$(6)\quad V_2 = \frac{1}{K_T} \log \frac{P_{T2}}{P_{O2}}.$$

If we subtract equation 5 from equation 6 and combine with equation 4, we get

$$(7)\quad V = \frac{K_T}{K_D} \left(\frac{1}{K_T} \log \frac{P_{T1}}{P_{T2}} - V_2 + V_1 \right)$$

It will be seen that this formula differs from that of Dr. Grant's equation 1 only by the factor $\frac{K_T}{K_D}$. Grant's formula represents the assumption, as a first approximation, that $K_T = K_D$. Now measurements of these two coefficients by the

same investigator on the same eye have not so far been reported. However, Dr. Grant has been making such measurements on enucleated human eyes, and he says that he has been finding no great difference between K_T and D_D, and that the ratio $\frac{K_T}{K_D}$ is therefore not far from unity.

In all probability, this ratio changes little, if at all, from eye to eye. It enters into Dr. Grant's data merely as a scale factor and does not significantly influence the relative values which he gets in comparing different eyes. It will become a matter of crucial importance only if data compiled by Dr. Grant's method are compared with those compiled by other procedures.

If we neglect this scale factor and analyze the items inside the bracket in equation 7, we come to matters of more immediate concern. The values P_{T_1} and P_{T_2} are taken from my tonometric calibration measurements, in which the eye tested was connected with open stopcock to a pressure reservoir. These "open-manometer" measurements show remarkably good reproducibility. My own data are in close agreement with those of Schiøtz of 50 yr. ago. Almost the same values are obtained on rabbit, cat, pig, and human eyes. Variations in corneal curvature and in corneal thickness, therefore, have no significant influence on the readings. The accuracy of the values P_{T_1} and P_{T_2} depends, consequently, almost exclusively on the accuracy of the tonometer-scale reading. Assuming that Dr. Grant can read his graphic record to 0.2 scale unit, the value of log $\frac{P_{T_1}}{P_{T_2}}$ may be assumed to be correct within ± 5%.

For K_T, Dr. Grant has used the estimated average value on normal eyes. In 1936 I published estimates of the value of K_T for 500 normal human eyes. The frequency distribution of these values follows an essentially normal frequency curve, and the standard deviation can be readily estimated. Allowing for the fact that this standard deviation is partly the result of reading errors in tonometry, it can be concluded that in the normal population the use of the average normal value of K_T, instead of the particular value appropriate for each eye, yields an uncertainty in the item $\frac{1}{K_T} \log \frac{P_{T_1}}{P_{T_2}}$ of about ± 25%. Exact estimates of K_T for any single eye are difficult and require many measurements. Dr. Grant is not to be criticized for having used the average normal value as a first approximation.

The tables of values for V_1 and V_2 were obtained by direct experimental measurements on 10 human eyes and on 60 cat and rabbit eyes. The mean values for the measurements on human eyes at various fixed pressures fell on a reasonably smooth curve, and resulting tables which were used by Dr. Grant appear to be solidly based. The experimental scatter in these measurements was, however, much larger than in determining the P_T values, and it became clear from an analysis of the data that the volume of the corneal indentation corresponding to a particular tonometer reading is very considerably influenced by variations in corneal curvature and thickness, even within the normal range. In taking the difference $V_2 - V_1$ between two readings on the same eye, the variability is somewhat reduced, but I should not feel that the value of $V_2 - V_1$ (uncorrected for corneal curvature and thickness) could be estimated closer than ± 15%. This would hold for eyes with clear corneas of the normal range of curvature. For edematous or scarred corneas, for buphthalmos or microphthalmos, no estimate whatever can be given at the present time.

If we include the reading errors of the measurement but still disregard the scale factor $\frac{K_T}{K_D}$, the estimated uncertainty in ΔV, due largely to normal variations in K_T and in corneal curvature and thickness, is, under favorable conditions, of the order of ± 20%.

Now we come to Dr. Grant's second equation. He estimates the "facility of outflow," designated by the coefficient C in the equation

$$(8)\quad C = \frac{\Delta V}{T(P_{T_{av}} - P_{o_1})}$$

The numerator on the right of this equation has an uncertainty of the order of ± 20%. In the denominator, T (the time in minutes) and $P_{T_{av}}$ can be determined accurately. P_{o_1}, however, involves all the uncertainties of tonometer calibration. The Schiøtz chart currently approved by the Committee on Standardization of Tonometers is based on a compromise between my own experimental findings and those of the half-dozen others who have attempted to calibrate this instrument during the last 50 yr. Dr. Grant has used my data. It is most gratifying that by the use of these data he gets generally consistent results, and this fortifies my own opinion that my calibration is a good deal closer to the truth than those of previous investigators. The strongest evidence is Grant's finding that on very prolonged tonometry, P_{T_2} approaches P_{o_1}, as it should when the intraocular pressure finally regains its initial equilibrium value. Incidentally, this affords a new and valuable method for tonometer calibration. The P_{o_1} values, however, are based on assumed average normal ocular rigidity. In case an eye deviates in its K_T value by the standard deviation from the average normal, the P_{o_1} values will be erroneous by approximately ± 15% and the $(P_{T_{av}} - P_{o_1})$ by at least ± 30%.

Since both the numerator and the denominator in the estimate for C (equation 8) are affected largely by uncertainties in the value of K_T for the particular eye measured, one might hope that these errors would tend to cancel themselves out. Unfortunately, this is not the case. If an eye has a rigidity greater than the average normal, then the numerator will be overestimated and the denominator underestimated. The two errors are, therefore, substantially additive, and the uncertainties in estimation of the coefficient of facility of outflow (C) correspondingly large.

Up to the present I have been considering uncertainties in the estimates in terms of the statistical measure: standard deviation. In a series such as that presented by Dr. Grant for normal eyes, the range of variation would be approximately double the standard deviation. On the basis of the factors so far enumerated, i. e., reading errors and normal variations in ocular rigidity and in corneal curvature and thickness, and if the facility of outflow were identical in all normal eyes, one would expect a range in the estimates of facility of outflow from about one-half the average value to about twice the average value. Dr. Grant finds his estimates for C in normal eyes to vary from 0.11 to 0.44, with an average of 0.22. The extremely close agreement of these figures with the estimate of expected range on the basis of the above analysis is largely fortuitous, but one is, nevertheless, justified in concluding that the true range of variation in the facility of outflow in normal eyes is probably very much narrower than that obtained by Dr. Grant. This is indeed an encouraging circumstance, for it indicates that as methods of estimating the facility of flow become more precise, it will be possible to give clinical significance to much smaller deviations than those found by Dr. Grant between normal eyes and eyes with uncompensated glaucoma. The early diagnosis of deep-chamber-angle glaucoma looms as a significant possibility. Furthermore, the conclusion that the normal range of variation in facility of outflow is relatively narrow greatly fortifies the clinical significance of the difference which Dr. Grant finds between the average reading on normal eyes and the average reading on eyes with uncontrolled glaucoma. It should be pointed out that in repeated measurements on the same eye most of the sources of error enumerated will be constant, and hence that quite small changes in facility of outflow may be detectable.

The third step in Dr. Grant's calculations is to use the facility of outflow and the intraocular pressure before tonometry to estimate the rate of flow of the intraocular fluid. In his first paper, he estimated the rate of flow, F, by

$$(9)\quad F = C\,P_{o_1}\,.$$

In his present paper, on the basis of experiments on enucleated eyes, he has made a slight modification:

$$(9A) \quad F = C\ (P_{o1} - 4)\ .$$

These equations assume that if the formation of intraocular fluid were stopped the intraocular pressure would drop to zero (equation 9) or to 4 mm. Hg (equation 9A). If one neglects the possible contribution of the osmotic pressure of plasma proteins, the intraocular pressure, if aqueous formation were stopped, should not drop lower than the episcleral venous pressure, which I shall designate P_V. Thus, the first approximation for the estimate of the rate of flow should be

$$(10) \quad F = C\ (P_{o1} - P_v)\ .$$

Admittedly, the pressure in the episcleral veins is hard to estimate. By methods which are not wholly satisfying, Goldmann estimates this pressure at about 10 mm. Hg. Löhlein gives similar figures, and both these authors believe that the P_V may differ substantially in glaucomatous, as compared with normal, eyes. Until measurements of P_V can be included in the clinical technique, I believe that estimations of F are hazardous.

It should be pointed out that if the P_V of normal eyes is the same as or higher than that of glaucomatous eyes, then Dr. Grant's method of estimating F would give relatively lower values in glaucomatous eyes than in the normal eye. Whether this would account for the whole of the differences that he finds remains uncertain, but on the basis of the present data the conclusion that the rate of flow is diminished in glaucoma seems to me extremely uncertain. Dr. Grant has suggested this conclusion with due reserve. I emphasize this point merely to warn careless readers of Dr. Grant's paper from disregarding his judicious reservations.

In connection with the significance of episcleral venous pressure, it should be pointed out that this pressure may well be raised during tonometry. The weight of the tonometer rests on the eyeball and must raise the intraorbital pressure. Assuming that the supporting orbital pressure operates over the area enclosed by the insertion, the anterior orbital fascia on the eye, a circular area of 15 to 20 mm. in diameter, then the rise in intraorbital pressure during tonometry will be between 5 and 10 mm. Hg. To what extent this will be reflected by a rise in episcleral venous pressure is uncertain. So far as this is a significant factor, it will enter as a correction for P_{O_1} in equation 8 and for P_{T_1} and P_{T_2} in equation 7. In view of Dr. Grant's finding that on very prolonged tonometric determination, P_{T_2} approaches the estimated value of P_{O_1}, the disregard of changes in orbital pressure during tonometry will not, in general, amount to a large error. It should be pointed out, however, that in some glaucomatous eyes with very small facility of outflow the pressure reading, P_T is found to rise during the first minute or two of tonometry. Such a paradoxical rise can most readily be accounted for by the gradual adjustment of the intraocular pressure to the change in episcleral venous pressure. At any rate, I should regard this as a more tenable hypothesis at present than the alternative that the application of the tonometer is some mysterious way may stimulate active secretion of intraocular fluid.

I should like to emphasize again that the analysis of sources of error in the measurements that I have made implies no criticism of Dr. Grant's very significant contribution. He has developed this method to the point at which it has already made a useful contribution to our clinical evaluation of the individual problems in cases of glaucoma and has very largely fortified the conclusion that the essential defect in all varieties of glaucoma is an obstruction of aqueous outflow. I believe that the estimate of the facility of outflow is, in the present state of development of this method, much more reliable than the estimate of flow in the undisturbed eye. Dr. Grant has been fully aware of the sources of error in measurements that I have enumerated and has stated his conclusions with due reserve. He deserves very great credit for having brought this method to the level of clinical serviceability and for having thereby opened a new and very important field in the analysis of the pathologic physiology of glaucoma.

DR. PAUL CHANDLER: Dr. Grant's clinical measurement of aqueous outflow has furnished us with one of the most valuable tools for the study of glaucoma which has been evolved in the last several decades. Perimetry, tonometry, and, to a less degree, measurements of visual acuity have long been the principal tools for the diagnosis and management of glaucoma, and doubtless they will continue to play the most important role. In the past two decades gonioscopy has made possible valuable contributions to knowledge of glaucoma, principally in the classification of the glaucomas. Gonioscopic studies have indicated that the mechanism of obstruction to outflow in glaucoma is of an entirely different nature in narrow-angle than in wide-angle glaucoma, that in the former the obstruction to outflow is due to block of the angle by forward displacement of the root of the iris, whereas in the latter the obstruction is evidently in the angle structures themselves. Dr. Grant's work has beautifully confirmed this conception. He has invariably found in narrow-angle glaucoma that when the iris periphery does not overlie the filtration area the facility of aqueous outflow is normal. In other words, if aqueous can gain access to the pectinate ligament, there is no obstruction to its escape, whereas in wide-angle glaucoma at all stages obstruction to outflow is present.

Thus, the classification of primary glaucoma into the narrow-angle and the wide-angle groups, as first suggested by Raeder (*von Graefes Arch. Ophth.* **112:29**, 1923), and further elaborated by Barkan (*Am. J. Ophth.* **24:768**, 1941), Sugar (*Am. J. Ophth.* **32:425**, 1949), and others, is proved to be valid. Once one accepts the essential difference in the mechanism in the two types of glaucoma, one can go on to a more intelligent selection of a particular type of treatment for a particular type of glaucoma.

In the glaucoma secondary to inflammation of the anterior segment of the eye, Dr. Grant has always found obstruction to outflow. When the tension falls while the inflammation is still active, though there is still obstruction to outflow, the lowered tension is found to be due to decreased formation of aqueous, presumably as a result of the opening of the blood-aqueous barrier.

It is good to have the ghost of hypersecretion as a factor in glaucoma finally interred. Dr. Grant has furnished conclusive proof that obstruction to outflow is the sole factor in the increased tension in glaucoma, and the whole problem is thereby that much simplified.

Tonography bids fair to supersede the various provocative tests for wide-angle glaucoma. Dr. Grant has consistently found a rate of outflow below normal, not only in early wide-angle glaucoma, when the diagnosis has been established by the presence of cupping, increased tension, or loss of field, but also in most instances in the fellow eye, in which the diagnosis of glaucoma has not been made by the usual clinical methods.

In the patients with progressive cupping and atrophy with tension always in the normal range, he has found some cases in which aqueous outflow is normal, indicating that the mechanism of the damage is to be sought in the optic disk or nerve. In other cases clinically similar, obstruction to outflow suggests that the condition is a true glaucoma, with the normal tension due to a low rate of aqueous formation.

Tonography should be a useful method for the evaluation of new drugs for the treatment of glaucoma. Drugs may one day be discovered which will lower the tension in glaucoma by reducing the rate of aqueous formation.

It is a great personal satisfaction to me to have this opportunity publicly to congratulate Dr. Grant on developing and applying this new method, which promises to add so much to our understanding of the problem of glaucoma.

DR. PETER C. KRONFELD, Chicago: The method of clinical investigation which Dr. Grant has so aptly named tonography has been a special concern of mine for over 20 yr. Reading Dr. Grant's paper and listening to his masterful presentation have made me so excited that I find it hard to keep my feet on the ground. I find it difficult to distinguish between what has been established already and what we hope to establish in the next five years.

The observations of Dr. Grant, as well as those of Drs. Moses and Bruno, and those of Dr. Philip Shane, of St. Louis, which were reported to us at a meeting of the Chicago Ophthalmological Society a month ago, as well as my own observations in this field, are so similar that I think we have the right to speak of established facts.

The principal established fact is the greater resistance to outflow characteristic of the chronic wide-angle glaucoma. From the data available at this time, it is highly probable that the course of glaucoma correlates better with this coefficient of outflow than with the tension levels determined by single or repeated, or even frequently repeated, tonometric measurements. In other words, it seems to me that tonography is at the moment the most reliable tool in the follow-up study of glaucoma. Because of the slow evolution of many forms of glaucoma, it will take years before the tonographic characteristic of all types and phases of glaucoma will be established, but Dr. Grant has laid a sturdy foundation.

By a mathematical analysis, which entails certain simplifying assumptions, Dr. Grant has shown that tonographic data permit one to make estimates of the second factor in fluid exchange of the eye, namely, the rate of formation of the most minute volume of the aqueous. Variations in this factor have always played an important part in the clinician's attempt to explain the mechanism of certain glaucomatous situations. Now, for the first time, I believe, in the history of ophthalmology, we have a simple way of estimating that rate of formation or cessation of secretion, and I should like to cite a striking instance of an anomaly of that rate of formation. It concerns a postoperative state, namely, a state of a very low ocular tension after cyclodialysis—and before I introduce the case of cyclodialysis, I shall note the case of the tension after a trephination. A patient has been operated on for chronic wide-angle glaucoma by the trephining method and has what is generally considered a good result, with a beautifully filtering bleb, tension between 13 and 15 mm. Schiøtz, and good maintenance of visual function. Such a patient, if tested by Dr. Grant's method, proves to have a coefficient of outflow that by far exceeds the coefficient of outflow of the normal eye. In other words, fluid runs out of that eye with much greater ease than it runs out of one's own eye. The rate of formation of aqueous in that eye is slightly, perhaps at times moderately, diminished, but one can, by Morton Grant's method, arrive at a figure for the rate of formation which is just a little below normal.

Now, I shall consider an eye which, also for glaucoma, has had a cyclodialysis, and in which tensions vary from 4 to 8 mm. (Schiøtz); in other words, on one day the tension is 8 mm., and two days later it may be 4 mm. That patient, if tested tonographically, has a coefficient of outflow of either normal or slightly below normal, magnitude. In other words, the superciliary cleft is functioning, and one has a right to assume that, with a standard of outflow, this superciliary cleft functions almost as well as, or in a manner similar to, the normal Schlemm system. However, if that patient is examined on a day when his tension is only 4 mm. and the tonometer is left on the cornea for five minutes, no coefficient of outflow is obtained. In other words, the eye seems suddenly to maintain its low tension. I believe that since on the preceding day it was demonstrated that this eye had a mechanism of outflow and since the cleft is open—wide open—on both days, there is only one conclusion, namely, a greatly reduced rate of formation of aqueous.

There is another method by which estimates of the rate of formation have been tried, and that is the fluorescence method of Goldman. Goldman, with this method, has arrived at the same conclusion, namely, that in cyclodialysis, especially, very low levels of tension are accomplished, and that a reduction in rate, not a cessation of fluid formation, is an important factor.

Dr. Andrew deRoetth Jr., New York: At the Institute of Ophthalmology in New York, Dr. Neissen and I have also been working on the aqueous flow. We made about 250 tests on approximately 200 eyes. Half of the eyes were normal; half were glaucomatous. Of the 100 normal eyes, about nine, or 9%, had the

coefficient of aqueous outflow in the abnormal, that is, the low, range, meaning that the coefficient was below 0.15. Of the 100 glaucomatous eyes, about 30 were without treatment—with no medication at all. Of these 30 glaucomatous eyes, the chronic noncongestive type, as Dr Grant has also shown, fell in the group with low, abnormal aqueous outflow. However, most of the glaucomatous eyes of the congestive type, when they were examined between the congestive attacks, that is, in a quiescent phase, showed a normal coefficient of aqueous outflow.

In more than half the 70 glaucomatous eyes receiving mild medication, although the tension in most of them was well controlled, the aqueous outflow fell in the low, or abnormal, range. Therefore, if this aqueous outflow is any criterion of the success of our treatment of glaucoma as we know it at present, we are in a sorry state.

I should like to thank Dr. Grant for showing us this extremely interesting and, I believe, very useful diagnostic test.

DR. K. W. ASCHER, Cincinnati: I wish to express my admiration for Dr. Grant's method, as well as for his presentation. I can only ask a question, which I do not expect to be answered by any of the discussers today, but which I hope will be answered in the future, perhaps years, perhaps decades, from now.

You, Dr. Grant, and everyone working in your field, has stated what we have accepted or assumed for years, that the main factor in glaucoma, in its etiology, is retention of aqueous, impediment of aqueous outflow. My question is this: Where does this impediment take place? There are three main possibilities: (1) where the fluid enters the canal of Schlemm, the trabecular region; (2) where the fluid leaves the canal of Schlemm, the outlets, unfortunately called collectors—they are not collectors, but distributors, of the aqueous humor from the canal into the ciliary veins—and (3) these superficial veins, which finally take the intraocular fluid away.

DR. THOMAS M. D'ANGELO, Flushing, N. Y.: I should like to ask Dr. Grant how he arrived at a measurement of the intraocular pressure in terms of millimeters of mercury.

DR. W. MORTON GRANT, Boston: I wish to thank all the discussers for their contributions and the information that observations of this nature by others are in accordance with those which I reported.

The question about millimeters of mercury of intraocular pressure I can nicely pass to Dr. Friedenwald.

EVALUATION OF THE SURGERY OF CONGENITAL CATARACTS

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IN THE textbooks of ophthalmic surgery very little space has been devoted to a consideration of congenital cataracts. In recent years, however, and especially since the recognition of the rubella cataract, new interest in the subject has developed. Care of congenital cataracts is clearly a matter of first importance, to the community as well as to the patient; and this fact suggested that an attempt to evaluate the various surgical procedures currently in practice might serve a useful purpose.

Congenital cataract is usually not discovered until the child is several weeks or months old, and partial cataract which leaves some vision intact may be overlooked for an even longer time. The very narrow pupils of newborn babies, their habit of sleeping a good deal, and their inability to fix very often obscure the fact that they do not see.

Certain forms of congenital cataract show a hereditary tendency. Marner [1] reported on a family in which the occurrence of cataract could be traced back to 1780, through eight generations. The cataract descent was dominant, as apparently is usually the case. As often happens, the type did not run true throughout the family; the zonular cataract was the commonest, but central, anterior polar, stellate, and combined forms were also observed.

Falls [2] and other observers have shown that in approximately 50% of all cases of congenital cataract other ocular defects are present; these include amblyopia, nystagmus, aniridia, choroidal and retinal changes, and strabismus. Many babies with cataract show other, general congenital anomalies. Mental retardation occurs in a fairly high percentage and, according to Krause,[3] may not make its appearance until the child is 4 yr. of age or more. It has been held that the mental retardation in cases of congenital cataract is due to the lack of vision, and there is no doubt that in some instances restoration of vision has apparently had a very beneficial effect on the child's mentality. Other children with congenital cataract, however, for whom nothing could be done to restore vision have shown no evidence of mental deficiency.

It has long been recognized that the prognosis of surgical intervention in cases of congenital cataract must be guarded. As early as 1805 it was stated by Ware [4] that

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1. Marner, E.: A Family with 8 Generations of Hereditary Cataracts, Acta ophth. **27**:537-551, 1949.

2. Falls, H. F.: Developmental Cataracts, Arch. Ophth. **29**:210-223 (Feb.) 1943.

3. Krause, A. C.: Congenital Encephalo-Ophthalmic Dysplasia, Arch. Ophth. **36**:387-444 (Oct.) 1946.

4. Ware, J.: Chirurgical Observations Relative to the Eye, London, J. Mawman, 1805, p. 2.

operation was "not so certain a cure for cataract in children as in persons of a more advanced age." Moreover, in view of the inevitable operative risks, e. g., of anesthetic accident, postoperative infection, and surgical complication, congenital cataract surgery should be undertaken only after the most careful consideration. The type of operation to be performed must then be decided upon, and to this end a thorough knowledge of the various types of cataract encountered is of first importance.

CONSIDERATIONS IN CONGENITAL CATARACT SURGERY

Indications for Surgical Intervention.—Although it is difficult to lay down fixed rules, in general it can be said that surgical measures should be resorted to when the visual acuity is so reduced that the normal use and development of the eyes are impossible. When the visual acuity is 20/50 or better, surgical intervention is not indicated. In babies, in whom the visual acuity cannot be measured, the indications given by Chandler [5] form a sound working basis; Chandler feels that surgical treatment is indicated in those infants in whom bilateral complete cataract is present at birth or develops shortly thereafter, and in those in whom there is severe bilateral involvement without complete opacification. When there are bilateral dense central opacities and useful vision can be obtained only by dilating the pupil, surgical intervention is also indicated. It is not indicated in those cases in which there is only mild involvement of one eye, even though the other shows extensive opacification.

In borderline cases, in which there is moderate involvement of both eyes, one must be guided by the way the child is getting along in school, bearing in mind that it is unwise to hurry into surgery. If the child is not amblyopic, it is safe to wait until vision can be determined accurately. As noted above, surgical intervention is contraindicated when the vision is 20/50 or better. In zonular cataracts there is a tendency for the opacity to increase in density over a long period, so that it is not uncommon for serious visual difficulty to develop at puberty or thereabout. Thus, even though at the time of the initial examination the vision is such that operation is not indicated, the patient should not be told he will never need surgery, since at a later date surgical intervention may definitely be called for. Incidentally, the visual prognosis for surgery in the average case of zonular cataract is excellent.

Age at Which Operation Should Be Performed.—There is considerable difference of opinion as to the age at which it is best to operate for congenital cataract. Kirby [6] stated the belief that if operation is indicated it should be done early; he has reported good results from needling in babies only a few months old. Falls [3] recommends operating on one eye when the child is 6 mo. old if complete bilateral cataract is present. If, on the other hand, the cataracts are incomplete and the child has sufficient vision to enable him to get around, Falls is inclined to wait until the age of 3 or 4 yr. While Treacher Collins [7] advised early operation, he stated that he was inclined to wait until the child was 10 mo. old, when the eyes are larger and

5. Chandler, P. A.: Surgery of the Lens in Infancy and Childhood, A. M. A. Arch. Ophth. **45**:125-138 (Feb.) 1951.

6. Kirby, D., in The Eye and Its Diseases, edited by C. Berens, Philadelphia, W. B. Saunders Company, 1936, p. 565.

7. Collins, Treacher E.: Developmental Deformities of the Crystalline Lens, Ophthalmoscope **6**:577-663, 1908.

the anterior chamber is deeper. Shapland,[8] Knapp,[9] Owens and Hughes,[10] and others are inclined to wait until the child is 2 yr. old or more, as in their experience the results seem to have been poorer when operation was performed at an earlier age. These reports of unfavorable visual results may be misleading, however, for in cases of bilateral complete cataract, in which early operation is indicated, nystagmus and other congenital anomalies often are also present. In this event, even if the surgical result is good, the visual result may be very poor, and not to be compared with the results obtained when these other ocular anomalies are not present. Fuchs [11] reported that the earlier the operation, the better the visual results. It is my own rule to operate on the first eye at 6 mo. if the cataracts interfere with fixation, in the hope that by establishing fixation nystagmus may be prevented, and to operate on the second eye sometime in the third year. From the foregoing review, it is apparent that, although there is no unanimity of opinion, most authorities feel that if fixation is incomplete one cataract should be operated on before the end of the first year.

Visual Prognosis.—The visual results from extraction of congenital cataract are much poorer than those following extraction of senile cataract, and in discussing the situation with the parents one must always be guarded in making the prognosis with respect to vision. It is indeed most important that the visual possibilities be explained to the parents before operation, so that they will understand and not be disappointed when the final vision is considerably less than 20/20. Falls [2] found that 53% of his series achieved a visual acuity of 20/100 or better and that 9% achieved 20/200. For all practical purposes 17% were blind. Reading vision of Jaeger 4 or 7 or better was obtained in only 17%, and no patient with nystagmus had a final vision of better than 25/50. Owens and Hughes [10] found that, although an acuity of 20/70 or better was obtained in only 11% of the eyes with associated ocular defects, 20/70 or better was obtained in 62.4% of the eyes without other ocular defects. Vision of less than 20/200 was the final result in 42.5% of the eyes with other defects, but in only 18.5% of the eyes without other defects. There were associated ocular defects in 56% of their series, a figure corresponding roughly with the generally accepted 50%. These figures would seem to establish that the presence of other ocular defects is the most important cause of poor vision after operation. As noted above, the children for whom early operation is indicated have a higher percentage of these defects, and this, probably more than the early age, accounts for the poorer visual results in the children operated on before they are 2 yr. old. As Owens and Hughes concluded, the relatively poor visual results after extraction of congenital cataract are attributable to either gross or obscure associated ocular defects.

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8. Shapland, D. C.: Retinal Detachment in Aphakia, Tr. Ophth. Soc. U. Kingdom **54**:176-196, 1934.

9. Knapp, A.: Operative Prognosis of Congenital Cataract, Arch. Ophth. **32**:519 (Dec.) 1944.

10. Owens, W. C., and Hughes, W. F.: Results of Surgical Treatment of Congenital Cataract, Arch. Ophth. **39**:339-350 (March) 1948; Tr. Sect. Ophth., A. M. A., 1947, p. 228-241.

11. Fuchs, E.: Festschrift der Konigl., Zagreb, Jugoslavia, Universität-Augenklinik, 1928, p. 80.

SURGICAL PROCEDURES

The ideal operation for the removal of congenital cataract would meet the following requirements:

1. It would be a single procedure providing for the removal of the major portion of the lens, so that the rest could absorb.

2. There would be no interference with the pupil, and the danger of incarceration or adherence of the iris to the wound would be minimal.

3. There would be no interference with the posterior capsule and the vitreous.

4. The danger of glaucoma would be minimized.

In attempting to evaluate the relatively few operations which are in general use, it would seem advisable to review briefly the technique of each procedure before discussing its advantages and disadvantages.

Optical Iridectomy.—Optical irridectomy has been recommended in cases of zonular or anterior polar cataracts in which dilation of the pupil improves vision to 20/40 and in which the opacity is central. Its purpose is to alter slightly the position of the pupil; thus only that portion of the iris at the pupillary border should be excised. Experience has shown that removal in the inner lower quadrant of the iris gives the best results.

Technique: As the periphery of the iris must be preserved for optical reasons, a keratome incision is made a little inside the limbus, below and nasally. The smallest possible fold of iris is grasped at the pupillary margin and is drawn out and cut off at the tip, the blades of the DeWecker scissors being held perpendicularly to the corneal incision. A coloboma limited to the pupillary border of the iris is thus produced.

Results: The complications of this procedure are infinitely fewer than they are in operations in which the lens is removed, but the results are almost always disappointing, especially if the iridectomy is performed late, when there are often an accompanying nystagmus and amblyopia. Inasmuch as other procedures give so much better opportunities for good vision when the eye is capable of it, there would seem to be little justification for enlarging the pupil unnecessarily. Chandler [5] reported one very favorable result.

Discission.—Discission, in one form or another, is the most popular and widely used operation at this time. Its purpose is to obtain a deep penetration of the lens without penetration of the posterior capsule and vitreous; that is, there should be no through-and-through perforation of the lens. The Bowman knife-needle and the sickle-shaped Ziegler modification of the original Hayes knife are most commonly used.

Technique: The operation has been described by Spaeth [12] and others, but the best description is to be found in Meller's "Ophthalmic Surgery." [13] The knife-needle perforates the conjunctiva and then the cornea to the outer side of the limbus at about the horizontal meridian, and is then pushed forward and downward until it reaches the lower margin of the pupil. With the corneal perforation acting as a

12. Spaeth, E.: The Principles and Practice of Ophthalmic Surgery, Ed. 3, Philadelphia, Lea & Febiger, 1944, p. 610.

13. Meller, J.: Ophthalmic Surgery, edited by W. Sweet, Philadelphia, P. Blakiston's Son & Co., 1923, p. 226.

fulcrum, the handle of the instrument, inclined at an angle of about 45 degrees with the capsule, is moved from below upward through an arc of about 90 degrees, the blade cutting through the anterior capsule and the deeper lens structures.

The handle is now depressed and the knife point brought to the inner margin of the dilated pupil and entered through the capsule in the horizontal meridian. The handle is then raised through an arc of 45 degrees, and, with the corneal perforation still acting as a fulcrum, a horizontal incision is made through the capsule. To keep the point from sinking too deep and injuring the posterior capsule, the needle is withdrawn slightly while the cut is made and is finally pulled out of the eye quickly in the same direction in which it was entered. A crucial incision is indicated, as with only a single incision closure of the capsule would frequently occur.

Atropine is to be used postoperatively and should be continued for some time after the lens has absorbed to avoid occlusion of the pupil. The discission may be repeated if absorption ceases, owing to the folding-over and healing of the capsule.

Results: The end-results are usually good. Discission usually requires a number of operations, however; and this constitutes a real disadvantage from the parents' viewpoint. It has been stated that in some instances as many as 17 or 18 operations have been needed to achieve a good opening or good visual results.

Contraindication: A needling should never be done in the presence of a small pupil. If the pupil is small with atropine before operation, it will most certainly be smaller after operation, and this will constitute a seriously complicating factor.

Complications: The following complications may arise from simple discission: (1) cessation of absorption, as the result of postoperative irritation from the folding-over of the capsular tags; (2) posterior synechiae with occlusion of the pupil, usually in cases in which the pupil cannot be dilated; (3) prolonged postoperative low-grade iridocyclitis; (4) organization of capsular tags and remnants into a dense membrane, and (5) glaucoma, resulting from (*a*) swelling of the lens fibers, (*b*) occlusion of the pupil, (*c*) blocking of the angle by the swollen cortex and (*d*) blocking of the pupil by vitreous.

Ziegler's V-shaped Through-and-Through Discission of the Lens.—This operation, proposed by Ziegler in 1921,[14] but with which I myself have had no experience, still has many advocates, e. g., Wiener and Alvis.[15] Wilder,[16] on the other hand, has condemned it.

The commonest complications of this operation have been (1) delayed absorption, (2) disturbance of the vitreous, permitting its entrance into the anterior chamber, and (3) glaucoma. Chandler[5] has pointed out that if glaucoma should supervene and a linear extraction be attempted to relieve it, the danger of loss of vitreous, with its attendant complications, would be very great. Spaeth[12] has stressed the possibility of the late development of chronic iridocyclitis and detachment of the retina.

14. Ziegler, S. L.: Complete Discission of the Lens by the V-Shaped Method, J. A. M. A. **77**:1100 (Oct. 1) 1921.

15. Wiener, M., and Alvis, B. Y.: Surgery of the Eye, Philadelphia, W. B. Saunders Company, 1939, p. 54.

16. Wilder, W. H.: The Operative Procedures and Methods of Handling Juvenile Cataract, Tr. Am. Acad. Ophth. **33**:113-131, 1928.

Moncreiff's Discission.—A report of Moncreiff's modification [17] of the discission was published in 1946 and is the only new procedure to have been introduced for some time.

Technique: A needle incision through the anterior capsule into the cortex is followed by multiple incisions in all directions down to the nucleus. This is repeated until the anterior cortex and capsule are reduced to shreds. The nucleus is then cut into several fragments. When the knife is withdrawn, a small amount of aqueous is allowed to escape. With an anterior chamber irrigator, an attempt is made to wash all of the cortical material from the remnants of the capsular sac into the anterior chamber.

Results: Only a limited number of cases in which the lens was subjected to this procedure have been reported, but Moncreiff [18] states that the operation in the hands of others has also given good results. In only one case has there been a report of increased tension. The operation was intended only for children under 6 yr. of age, but Moncreiff operated on both eyes of a child 8 yr. of age and complete absorption required three months instead of one.

Callahan [19] has used Moncreiff's technique in 15 cases over a period of two years and believes it to be the method of choice, its value lying in (1) the thorough maceration of the cortex and nucleus, which is not achieved by the usual cruciate incision through the anterior half of the lens, and (2) the washing of the nucleus toward the cornea, which allows more surface area for absorption. Callahan found that a "second discission" on the same eye was rarely necessary and that there were no complications.

From the few reports available at this time it would seem that further observation on this procedure is clearly indicated and that its ultimate evaluation must await further experience.

Intracapsular Extraction.—Intracapsular extraction has a very limited use in the surgery of congenital cataract. Falls [2] used the procedure in cases of shrunken, dense, membranous, or "hard" cataracts, and Malbrán and Tosi [20] used it, with disastrous results, in the case of disk-shaped cataracts.

Linear Extraction.—This is my personal choice of procedure in the average case of congenital cataract. Only one operation is required; absorption is rapid, and useful vision is obtained in a very short time.

Technique: Chandler [5] and others prefer to make the incision at the limbus under a conjunctival flap with a suture in the wound. My own choice of technique [21] is a slight modification of the procedure, described by Barkan [22] in 1932.

After the routine preoperative preparation and anesthesia, 2 drops of epinephrine hydrochloride (1:1,000) is injected at the limbus above, the open part of the needle being directed

17. Moncreiff, W. F.: Contributions to Surgery of Congenital Cataracts, Am. J. Ophth. **29**:1513-1522 (Dec.) 1946.

18. Moncreiff, W. F.: Personal communication to the author.

19. Callahan, A.: Personal communication to the author.

20. Malbrán, J., and Tosi, B.: Cataracta Anular Congenita, Arch. oftal. Buenos Aires **15**:543-558 (Nov.) 1940.

21. Cordes, F. C.: Surgery of Congenital Cataracts, Am. J. Ophth. **31**:1073-1084 (Sept.) 1948.

22. Barkan, O.: Procedure for Extraction of Congenital, Soft and Membranous Cataracts, Am. J. Ophth. **15**:117-124 (Feb.) 1932.

toward the limbus. After five or 10 min. the pupil is widely dilated, especially at the site of the impending incision; and a suture is placed in the superior rectus. The dilation of the pupil, resulting, as it does, from the contraction of the sympathetic fibers, persists when the anterior chamber is opened, and this keeps the iris out of the wound.

Prior to the incision a stab wound is made into the anterior chamber below and temporally to facilitate the injection of air after the completion of the operation. As an aid in locating the opening, the knife-needle is wiped on a piece of wet filter paper that has previously been impregnated with fluorescein, according to the method described by Kimura,[23] and the fluorescein in allowed to dry on the knife before the stab wound is made. This leaves a green stain along the course of the stab wound, which persists during the entire operation.

A keratome incision is made 1.5 to 2.0 mm. inside the limbus and parallel to the iris surface, to produce a valvelike opening. A large capsulotomy is now performed with Fuchs's capsule forceps. It is important to remember that the capsule forceps should be used only once, because of the danger of biting through the posterior capsule into the vitreous. The lens substance is now expressed and the anterior chamber washed out with isotonic sodium chloride solution.

With a small Luer syringe and a 28- or 29-gauge needle, air is injected through the previously made puncture wound. If the tip of the needle is dulled a little, it has less tendency to catch in the course of the puncture wound. The air remains in the anterior chamber for several days and prevents the iris from coming into contact with the keratome wound in the cornea, and thus prevents the formation of anterior synechiae. The long-continued use of atropine after operation is important.

Contraindications: The Barkan type of linear extraction is not indicated (1) in cases in which the pupil cannot be dilated, in which a linear extraction with full iridectomy should be performed, and (2) in cases of membranous or other thin types of cataract, in which there would be danger of vitreous loss after the use of the capsulotomy forceps.

Combined Discission and Linear Extraction.—In this procedure, which some surgeons prefer above all others, a fairly extensive discission of the anterior capsule is performed. The eye is then kept under observation for several days, until the lens material is sufficiently disintegrated to permit easy removal by linear extraction, which can be done by the Barkan technique. For reasons given above, no attempt should be made to remove pieces of the anterior capsule, because of the danger of vitreous loss. According to Chandler,[5] when a limbal incision is made, a peripheral iridectomy is always indicated. The usual postoperative regimen is followed.

Results: The results of this operation are among the best. It has only two disadvantages: 1. Two operations are required, and this is a serious objection to the parents. 2. There is danger of acute glaucoma, especially in patients of the adolescent age group, which would necessitate an emergency operation.

Iridectomy and Linear Extraction.—In cases in which it is impossible to dilate the pupil well prior to operation, or in which operation on the other eye has shown that it is impossible to keep the pupil well dilated postoperatively, a full iridectomy is indicated. The rubella cataracts usually fall into this category.

Technique: A 5-mm. keratome incision is made at the limbus. The iris is then grasped about midway between its root and the pupil, in as small a bite as possible. The iris is pulled out, and the iridectomy is done with the scissors at right angles to the incision. The capsulotomy is now performed and the extraction completed in the usual manner. Atropine is administered after operation.

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23. Kimura, S. J.: Fluorescein Paper, Am. J. Ophth. **34**:444-446 (March) 1951.

COMPLICATIONS OF CONGENITAL CATARACT SURGERY

Complications of Linear Extraction.—The complications discussed in the following paragraphs refer to all types of linear extraction.

1. Delayed Restoration of the Anterior Chamber, with Formation of Peripheral Anterior Synechiae: This complication can be prevented if the incision is made at the proper angle, so that the opening is valvelike, thus assuring rapid closure and healing of the operative wound. Furthermore, the injection of air into the anterior chamber restores it before the patient leaves the table. Barkan [23] stressed the importance of this point.

2. Anterior Synechiae with the Pupil Drawn Up: This complication can usually be avoided if the technique outlined above is carried out in detail. The injection of air is an especially important factor. Care should be taken not to inject too much air, however, as glaucoma may be induced and may persist as long as 48 hr.

3. Occlusion of the Pupil: This complication may occur in cases in which the pupil will not dilate well or in which the postoperative use of mydriatics has been discontinued too soon. It rarely occurs in cases in which an iridectomy has been done. The necessity of long-continued use of mydriatics, even in cases in which an iridectomy has been done, cannot be stressed too much.

4. Membrane Formation: This complication may result from an inadequate opening in the capsule with associated iritis. It may be associated not only with linear extraction but with any of the other types of congenital cataract surgery. In doing the capsulotomy, it is important to make a large opening, although it must be remembered that use of the Fuchs capsule forceps must be limited to one attempt. If the forceps are reintroduced, a piece of the posterior capsule which has been displaced forward will in all probability be grasped and vitreous will be lost. As already stated, another cause of membrane formation is an inadequately dilated pupil associated with iritis.

5. Vitreous Loss: This occurs infrequently if the proper precautions are taken. The lens material should be milked out with a gentle stroking motion, caution being exercised not to use too much pressure. After the cortex is milked out with a spoon, the anterior chamber should be washed out with saline solution. All cortex that can be washed out will come out quickly, so that prolonged lavage not only is unnecessary but may result in loss of vitreous. For the same reason, no attempt should be made with forceps to remove cortex that has not washed out; the risk of loss of vitreous is too great. An important factor in avoiding loss of vitreous is in knowing when to stop. Cortex does absorb; so it is the part of wisdom not to do too much.

6. Glaucoma: Very rapid swelling of the cortical fibers, with blocking of the angle of the anterior chamber, may induce glaucoma. When this complication occurs within the first four days, opening the wound with an iris repositor and washing out the cortex controls the glaucoma. If a Barkan type of linear extraction is done, epinephrine should be injected at the limbus at the time of operation, and air should be injected at the completion of the operation. This complication has occurred three times in my personal experience.

An inadequate capsule opening, resulting in acute swelling of the lens, may also produce acute glaucoma. In this event, a second capsulotomy and lavage of the cortex is remedial.

Importance of Postoperative Use of Mydriatics.—The prolonged use of atropine or scopolamine will greatly reduce the frequency of many of these complications. If the mydriatic is discontinued before all the cortex is absorbed, occlusion of the pupil or posterior-synechia formation is very likely to occur. It is well to continue the mydriatic at least every other day for two months after the eye seems to have cleared entirely. It is most important that the parents know how to instill the drops, and to this end it is wise to have them demonstrate their technique in the office, so that it can be corrected if necessary.

Special Complications of Congenital Cataract Surgery.—Two complications of congenital cataract surgery warrant special consideration.

1. Detachment of the Retina: This is a complication that occurs late in a definite percentage of cases. The causative factors are not well understood. Spaeth [12] pointed out that detachment may occur late after the Ziegler through-and-through discission, and Shapland [8] drew attention to the frequency of detachment after needling. In Shapland's series the detachment occurred after an average interval of about 24 yr. in 33 of a total of 40 cases. Moore [24] found that detachment occurred more frequently after the needling operation for soft cataract than after other procedures. Knapp [9] was under the impression that eyes with atypical forms of congenital cataract and eyes in which the cataract showed signs of degeneration were particularly subject to detachment. He concluded that detachment occurred because of defects in the structure of the eye, but that its development might be accelerated by operation on the cataract. Chandler [5] found that the more the vitreous was disturbed, especially if it was allowed to come forward into the anterior chamber, the greater the danger of late detachment of the retina. This apparent association between detachment of the retina and disturbance of the vitreous should certainly be kept in mind when the type of operation to be used is under consideration.

2. Glaucoma Resulting from Blocking of the Pupil by Vitreous, and from Filling of the Anterior Chamber by Vitreous: An excellent discussion of this complication is to be found in Chandler's John E. Weeks Lecture.[5]

This cause of glaucoma is often overlooked because of the difficulty of examining such young patients under the slit lamp. While it may occur after linear extraction when there has been loss of vitreous, it is seen most commonly after repeated discissions. When the vitreous is cut into, it comes forward and blocks the pupil; the vitreous is then forced into the anterior chamber and at times completely fills it. Chandler feels that this is the mechanism that causes the gross peripheral anterior synechiae not infrequently seen in patients who have had multiple discissions. The recommended treatment is transfixion of the iris or iridectomy.

This complication can usually be avoided if the vitreous is disturbed to the least possible extent and if one adheres without exception to von Graefe's dictum never to do a needling in the presence of a small pupil. Chandler feels that when a discission is required and the pupil is small, an iridectomy or a peripheral transfixion of the iris must be done at the time of needling.

Late Postoperative Complications and Surgical Procedures.—1. After-Cataract (secondary cataract).—In a certain percentage of cases postoperative opacification

24. Moore, F., in discussion on Greeves, R. A.: Diathermy in Ophthalmology, Tr. Ophth. Soc. U. Kingdom **53**:487, 1933.

of the posterior capsule develops and requires surgical intervention. For this condition, or for any membrane obliterating the pupil, I prefer the Wheeler discission. An excellent description of this procedure is to be found in Wheeler's original article.[25]

Technique: A very sharp Wheeler knife is pushed through the cornea 2 mm. from the limbus (usually in the vertical meridian) into the anterior chamber, and the point is then advanced until it is just beneath the iris at the pupillary margin opposite. The knife is then thrust through the membrane and the handle carried forward, the blade moving in an arc about the point of insertion through the cornea, which acts as a fulcrum. The wrist is kept stiff, and the knife handle is allowed to turn easily between the thumb and the index finger. As the handle reaches the vertical position, the knife is gradually slipped from the corneal wound. The importance of using a very sharp Wheeler knife cannot be stressed too strongly. Atropine is instilled afterward.

Complications: As summarized by Weeks,[26] the complications of surgical treatment of this secondary cataract are as follows: (*a*) Insertion of the knife too far back, or carrying it too far back in the process of withdrawing it, may cut the ciliary body. (*b*) Failure to engage the membrane may result in its being torn from its attachments below and in being pushed before the knife. This pull or drag may cause iridocyclitis. (*c*) If the membrane bends in front of the knife and the knife is held still a second, or a short cutting movement is made, the membrane may snap apart. (*d*) If the knife is not carried through its evolution deftly, the corneal wound may enlarge and vitreous follow the knife; this may cause a fistula. To avoid this complication, the opening should be cauterized by the actual cautery.

2. Occlusion of the Pupil by Membrane Formation: This complication may occur in cases in which there is a thick membrane composed of capsule and lens material, or a complicated membrane due to inflammation, organized exudate, or hemorrhage.

Technique: A keratome is pushed through the cornea just in front of the limbus until the incision is about 4 mm. in length. The keratome is then withdrawn, and DeWecker (or Berens) scissors are introduced into the anterior chamber, their blades being kept closed until they have passed the corneal wound. On entering the anterior chamber, the blades are opened 1 mm. or more, and the sharp tip of the posterior blade is pushed through the membrane gently. The blades are then carried downward, the one behind, the other in front, until the desired length of cut is assured. Deliberate closure of the scissors cuts the membrane, and the instrument is withdrawn.

This procedure is varied a little if the membrane has been shown by preliminary study to be very thick or tough. After the corneal incision, the tip of the keratome, which must be very sharp, is pushed through the membrane at its upper end, where it is usually thinner. If this is unsuccessful, a very thin cataract knife or a Wheeler knife will usually effect an opening, which will facilitate the entry of the DeWecker or Berens scissors. This procedure, of course, is to be avoided if possible, as it may

25. Wheeler, J.: Secondary Cataract Opening by Single Straight Incision: Iridotomy by Same Method, Am. J. Ophth. **8**:179-183 (March) 1925.

26. Weeks, W. W.: Surgery of the Eye, New York, School of Ophthalmology and Otolaryngology, M. Stewart, Sec., 1937, p. 49.

result in a presentation of vitreous in the wound, which will complicate the operation further. A preplaced corneoscleral suture, followed by injection of air, is also indicated.

3. Obliteration of the Pupil as a Result of the Iris Being Drawn into the Wound: According to Weeks,[27] an iridotomy should be performed when there is a complicated, lively (elastic) membrane to which the iris and tissues posterior to it are probably attached, or when the lens capsule is drawn up into a secondary cataract or into a traumatic corneal wound.

Technique: The tip of the discission knife is introduced into the anterior chamber, pushed through clear cornea 3 mm. from the limbus, and carried across horizontally at right angles to the drawn-up, stretched-out iris bands. The knife tip is then pushed through to the point of entry, the knife cutting through with a deliberate, short, sawing movement. The cut is usually 3 to 5 mm. in length. It widens somewhat as the cut is completed, and more so as the anterior chamber is formed and as a result of the use of atropine on subsequent days. The wound in the cornea is usually not large and is closed without incarceration of vitreous.

Complications: The knife must have a keen point and be very sharp. Care must be taken to cut exactly perpendicularly to the iris bands and not to use too much force or speed; otherwise, the iridodialysis, or the reactionary irritation of the iris and ciliary body, will set up an iridocyclitis. Hemorrhage may also be free, and its organization may nullify the desired result.

EVALUATION OF SURGICAL PROCEDURES

A review of the literature brings out some interesting findings with regard to the relation of the type of surgical procedure employed in the management of congenital cataract to the results achieved.

Falls [2] reported the results in a series of 132 cases, in which 71% of the eyes were treated by discission and 22% by discission combined with linear extraction. Of the patients treated by discission alone, 27% achieved a vision of 6/12 or better, and of those treated by discission and linear extraction combined, 55% secured a vision of 6/12 or better, indicating that the latter procedure produces the best visual results.

Horay [28] reported his results in 282 operations. Equal numbers of his patients were subjected to discission, linear extraction, and combined linear extraction and discission. The age of the patient played no part in the decision as to which type of operation was to be used. The best results were obtained with linear extraction, and the poorest, with discission. Horay expressed the belief that the opinion that operation should not be done during the first year was unsound, as his results were equally satisfactory when the operation was performed during the first year and when it was performed later. He attributed many of the failures of operation during the first year to other congenital anomalies. His choice of procedure was the combined discission and extraction performed at one sitting, irrespective of the age of the child.

27. Weeks.[26] p. 52.

28. Horay, G.: Über Staroperationen im Kindesalter, Klin. Monatsbl. Augenh. **74**:178-184 (Jan.-Feb.) 1925.

Owens and Hughes,[10] in a review of 231 eyes operated on at the Wilmer Ophthalmological Institute, found that linear extraction, or discission followed by linear extraction, produced better results than simple discission. They found, further, that the number of secondary operations necessary to clear the pupillary space was higher after simple discission than after linear extraction or after discission with subsequent extraction. They also made the interesting observation that complications occur with essentially the same frequency after extraction of senile cataract as after extraction of congenital cataract. The poorer visual results from congenital cataract surgery they attributed to gross or obscure associated ocular defects.

Bagley,[29] in an attemppt to evaluate the various surgical procedures for congenital cataract, studied the results in 87 eyes operated on at the Wilmer Ophthalmological Institute between October 1943 and November 1947. He found that the results following single or repeated needlings were significantly poorer than the results following needling with subsequent lavage or following linear extraction. The final visual result following linear extraction was statistically better than the result following needling and subsequent lavage.

Chandler [5] stated his choice of a procedure in bilateral complete cataract in infancy to be complete iridectomy with linear extraction. In simple linear extraction he always uses a peripheral iridectomy.

A review of the literature and personal experience would indicate to me that some form of linear extraction is the operation of choice in congenital cataract. If the pupil can be dilated easily preoperatively, the simple (Barkan) linear extraction would seem to be preferable. If there is any difficulty in dilating the pupil, however, an iridectomy followed by linear extraction is indicated. Additional advantages of the simple linear extraction are that it cuts down the total number of hospital days per patient and greatly reduces the anesthetic and operative risks involved.

Experience has shown, however, that no one operation can be recommended to the exclusion of all others. With a thorough knowledge of congenital cataracts and careful study of the case in hand, it becomes apparent that in certain instances procedures other than simple linear extraction are to be preferred. For example, in a case of membranous cataract in which there has been absorption of the lens parenchyma during intrauterine life, so that the anterior and posterior capsules collapse to form a thin, gray-white or chalky-white membrane, linear extraction would probably cause loss of vitreous and other complications. In this situation the Wheeler type of discission is indicated. If by chance the membrane is very tough, so that the knife-needle fails to cut it, the DeWecker or Berens scissors should be employed.

In the case of posterior polar cataract in which the major opacity is confined to the posterior capsule, and which represents a persistence of the fibrovascular sheath of the lens, there is usually a disturbance of the lens fibers directly beneath the opacity. In this event, a linear extraction, to be followed by a discission through the posterior capsule, seems to be the operation of choice. In view of the frequency of other anomalies in association with cataracts of this type, the surgical prognosis must be guarded.

29. Bagley, C. H.: Congenital Cataracts, Am. J. Ophth. **32**:411-418 (March) 1949.

Disk-shaped cataracts consist of two types of lens substance, i. e., a central membranous portion, and a soft peripheral ring of clear lens substance. In one case of this type Treacher Collins [7] was able to separate the central plaque, which fell into the anterior chamber and remained there without reaction. Experience has shown, however, that both this procedure and discission in these cases are extremely difficult, and often impossible, and the disastrous results following attempted intracapsular extraction have already been mentioned. The procedure that Haro [30] found most useful was a discission of the soft cataract, followed later by a cutting of the membranous part with DeWecker scissors through a keratome opening.

SUMMARY AND CONCLUSIONS

1. It is important to remember that the surgical prognosis in congenital cataract is not as good as it is in senile cataract. In at least 50% of cases other congenital ocular anomalies may complicate the surgical procedure. In only approximately 50% is postoperative vision of 20/200 or better achieved, so that if a child has a vision of 20/50 the cataract should probably be left alone.

2. In view of the operative risks that are always entailed, operation on congenital cataract should be undertaken only after the most careful consideration.

3. If surgical intervention is indicated, linear extraction performed at one sitting is the operation of choice in the average soft cataract. If the pupil can be well dilated, the most desirable procedure is the simple extraction advocated by Otto Barkan, or some modification thereof. If it is difficult to dilate the pupil before operation, however, a linear extraction with full iridectomy is indicated. This applies particularly to the rubella cataract.

4. Injection of air into the anterior chamber at the conclusion of the operation is a very important factor in preventing anterior peripheral synechiae. In the simple linear extraction it prevents the formation of anterior synechiae between the iris and the incision.

5. While linear extraction is the operation of choice, it cannot be used in all cases. Careful study of each case, in the light of a thorough knowledge of the nature of congenital cataracts, will in some instances indicate that other procedures are advisable.

6. The importance of the use of atropine or scopolamine after any type of congenital cataract surgery, for as long as two months after the eye seems to have cleared entirely, cannot be overemphasized. If mydriatics are discontinued before all the cortex is absorbed, there is usually an occlusion of the pupil or posterior-synechia formation.

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30. Haro, E.: Hereditary Disk-Shaped Cataract: Report on a Family, with Microscopic Examination of the Eye, Arch. Ophth. **36**:82-100 (July) 1946.

DIVERGENCE PARALYSIS WITH INCREASED INTRACRANIAL PRESSURE

Further Observations

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AND
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RECENTLY we [1] reported three cases of divergence paralysis, in all of which the condition was associated with increased intracranial pressure. In addition, the literature on divergence paralysis was reviewed. For convenience, we shall summarize this paper before presenting our further observations.

In the literature, divergence paralysis is described in the following conditions: (1) inflammatory and toxic diseases of the cerebrum,[2] (2) cerebral hemorrhage,[3] (3) head trauma,[4] and (4) brain tumor. In the last category, seven cases were found in which the authors were able to verify the existence of a tumor of the posterior fossa either at operation or at necropsy. These seven cases were reported from four sources.[5] In all cases, there was evidence of increased intracranial pressure and concurrent divergence paralysis. In three of the cases,[5a] the tumor was removed, and the divergence paralysis disappeared as the papilledema diminished. We reported on three additional cases of increased intracranial pressure with divergence paralysis.[1] However, in only one of these three cases (Case 1) was the tumor of the posterior fossa. In one of the other two cases there was bilateral subdural hematoma, and in the other, serous meningitis. In all three of our cases, with surgical relief, the divergence paralysis disappeared with the clearing of the papilledema. All three patients made an uneventful recovery, with no return of either the papilledema or the divergence paralysis.

From the Neurosurgical service of Beth Israel Hospital.

1. Chamlin, M., and Davidoff, L. M.: Divergence Paralysis with Increased Intracranial Pressure, J. Neurosurg. **7**:539-543, 1950.

2. Duke-Elder, W. S.: Textbook of Ophthalmology, Vol. 4: The Neurology of Vision, Motor and Optical Anomalies, London, H. Kimpton, 1949, pp. 4175-4177.

3. Alger, E. M.: Paralysis of Divergence, Tr. Am. Ophth. Soc. **14**:665-667, 1916.

4. Bielschowsky, A.: Sog. Divergenzlahmung, Ber. deutsch. ophth. Gesellsch. **28**:110-124, 1901. Weed, H. M.: Divergence Paralysis Due to Head Injury, Tr. Am. Acad. Ophth. **39**:189-197, 1934. Savitsky, N., and Madonick, M. J.: Divergence Paralysis and Head Trauma, Arch. Neurol. & Psychiat. **53**:135-137 (Feb.) 1945.

5. (a) Savitsky, N., and Madonick, M. J.: Divergence Paralysis Associated with Tumor of the Brain, Arch. Neurol. & Psychiat. **55**:232-235 (March) 1946. Bender, M. D., and Savitsky, N.: Paralysis of Divergence, Arch. Ophth. **23**:1046-1051 (May) 1940. Lippmann, O.: Paralysis of Divergence Due to Cerebellar Tumor, ibid. **31**:299-301 (April) 1944. Robbins, A. R.: Divergence Paralysis with Autopsy Report, Am. J. Ophth. **24**:556-557, 1941.

In comparing our cases with the seven reported in the literature, we pointed out that the factors common to all 10 cases were increased intracranial pressure and divergence paralysis. Furthermore, divergence paralysis disappeared with successful operative relief of the increased intracranial pressure in our three cases, as well as in three of the reported cases, or in a total of six of 10 cases. We felt justified, therefore, in drawing attention to the possibility that divergence paralysis could be due to generalized increased intracranial pressure rather than to a focal lesion in the so-called divergence center in the midbrain.

Since the aforementioned report, we have had the opportunity of studying two more cases of divergence paralysis, which we now report. Only those findings which are pertinent to this paper will be reported.

CASE 1.—A young man (B. F.) had complained of headaches for several months and, recently, of diplopia. Tests of muscle function revealed typical divergence paralysis, with separation of the images starting at a distance of 1 ft. (30 cm.), the images being 4 ft. (120 cm.) apart at a distance of 20 ft. (6 m.). Mild but definite papilledema was observed. At operation a subdural hygroma was found on the left side and evacuated. The postoperative course was uneventful, with disappearance of the headache, papilledema, and divergence paralysis.

CASE 2.—A young woman (P. G.) had a two-months' history of headache and a two-weeks' history of diplopia. Examination revealed frank papilledema and typical divergence paralysis, with separation of images starting at 2 ft. (60 cm.), the images being 2 ft. apart at a distance of 8 ft. (2.4 m.). Ventriculographic examination revealed a mass in the left parietal area. Craniotomy verified the presence of a deep-seated parietal tumor, which could not be removed. However, with the decompression, the papilledema subsided, and with it the divergence paralysis disappeared.

We have been fortunate enough to hear from two of our colleagues who have had experience with similar cases.

In 1938, Kravitz[6] reported a case of temporoparietal tumor with papilledema and divergence paralysis. After surgical removal of the tumor, the first symptom to disappear was the divergence paralysis.

In October, 1950, Igersheimer[7] wrote to us about two cases of divergence paralysis with papilledema. In one case the diagnosis was pseudotumor cerebri (serous meningitis ?). After a number of lumbar punctures, the papilledema, headache, and divergence paralysis disappeared slowly. The other case was that of a brain abscess in the left temporal lobe, with papilledema and divergence paralysis. The abscess was tapped and partly excised. Three weeks later, there was still some papilledema but no headache or subjective diplopia, although slight divergence paralysis could still be demonstrated.

The case of Kravitz, the two cases of Igersheimer, and our two cases make a total of five cases of increased intracranial pressure with divergence paralysis and no evidence of a focal lesion in the posterior fossa. In our previous paper,[1] two of the three cases reported fell into the same category as these five cases, making a total of seven such cases. On the other hand, in our previous paper we cited from the literature seven cases of divergence paralysis and increased intracranial pressure

6. Kravitz, D.: Studies of the Visual Fields in Cases of Verified Tumor of the Brain, Arch. Ophth. **20**:437-470 (Sept.) 1938.

7. Igersheimer, J.: Personal Communication, Oct. 31, 1950, Bull. New England M. Center, to be published.

with a focal lesion in the posterior fossa, as well as one such case from our series, a total of eight cases of divergence paralysis with increased intracranial pressure and a focal lesion in the posterior fossa.

We have, therefore, a total of 15 cases of increased intracranial pressure and divergence paralysis, in 14 of which the diagnosis was confirmed either at operation or at necropsy. In eight of them a focal lesion was present in the posterior fossa, and in seven there was not. Therefore, the only factor common to all these cases of divergence paralysis was increased intracranial pressure. Furthermore, in 10 of the 15 cases there was definite improvement (complete disappearance in 9 cases) following relief of the increased intracranial pressure.

COMMENT AND CONCLUSIONS

The presence [8] or absence [9] of a true divergence center has been the subject of a great deal of discussion in recent years. While the question as to whether or not a true divergence center exists will probably go unanswered until more experimental and clinical work is done, we believe that our observations would argue against, rather than for, the existence of such a center.

The association of increased intracranial pressure with divergence paralysis seems to be a definite one. From a clinical standpoint, this association must be kept in mind. Thus, in cases of known increased intracranial pressure with diplopia, if a definite paralysis of one or more muscles is not easily found, divergence paralysis must be suspected and tested for. Conversely, if divergence paralysis is encountered, increased intracranial pressure should be suspected and sought, even in the absence of frank papilledema.

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8. Bruce, G. M.: Ocular Divergence: Its Physiology and Pathology, Arch. Ophth. **13**: 639-660 (April) 1935.

9. Scobee, R. G., and Green, E. L.: A Center for Ocular Divergence: Does It Exist? Am. J. Ophth. **29**:422-434 (April) 1946.

MODIFICATIONS OF THE ZEISS-NORDENSON RETINAL CAMERA

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NEW YORK

HISTORICAL BACKGROUND

THE VALUE of colored drawings of the fundus oculi, both in medical teaching and in the recording of pathologic conditions, was well recognized in the 19th century. However, with the improvement in photographic equipment and films during the 20th century, it became feasible to supplant the earlier drawings with actual clinical photographs of the eyegrounds, first in black and white and later in color film.

As early as 1862, Noyes, in America, had made attempts to obtain photographs of the fundus. Similarly, G. Bagneries experimented with elaborate equipment in Nancy, France, in 1889. Shortly thereafter (1891), Gerhoff developed a technique of flare-free photographs by immersing the eye in a water chamber with a plane front of glass.

Sigurd Hagen experimented with diascleral illumination, while Dimmer, in Vienna, obtained black and white fundus photographs with the use of cumbersome equipment.

It was not until 1915, however, that Nordenson, at the University of Uppsala, in Sweden, succeeded in achieving photographs of the eyegrounds covering a diameter of 40 mm. With further experimentation, the Zeiss-Nordenson flare-free retinal camera was developed in 1926, following the principles of the Gullstrand reflectionless central ophthalmoscope, i. e., the image-forming rays pass through the central area (the optically more important area) of the patient's pupil, while the illuminating rays enter the periphery of the dilated pupil and diffuse over the retina. In their respective passages through the refracting surfaces of the eye, the two beams travel in actually separate paths, thus insuring freedom from internal reflections and consequent haze on the final image.

In later models of the Zeiss-Nordenson camera, an aspherical objective was utilized with a focal length of 60 mm. and an aperture of 50 mm.

Since the Zeiss-Nordenson camera was conceived and manufactured in the period before color film was generally available, the first photographs [1] taken with the apparatus were in black and white (Fig. 1). When color film became available to the general public, certain technical problems relating to light source and practical film holders confronted those interested in obtaining photographs of the eyegrounds in natural color.

From the Department of Ophthalmology, New York University-Bellevue Medical Center.

1. von der Heydt, R.: Photography of the Fundus, Tr. Am. Acad. Ophth. **31**:439-441, 1926.

MODIFICATION OF THE FILM HOLDER

Replacement of the original single-sheet film holder or of the flimsy Rollex® back (which was not a Zeiss product) has been achieved [2] by the use of a standard inexpensive Eastman Kodak® Bantam® back. This camera back requires standard 828-size film in either black and white or color, and it can be loaded as simply and as rapidly as any box camera. There is no strain on or tearing of the film, since it lies in ordinary fashion in the focal plane within the camera, without having to

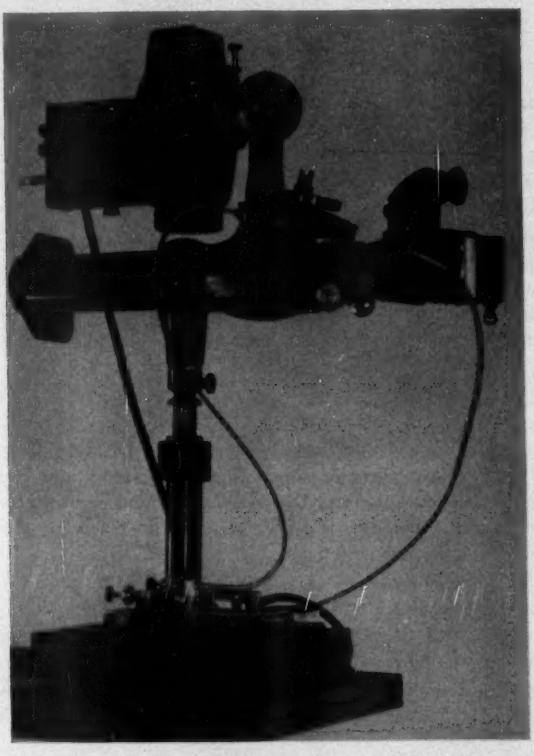

Fig. 1.—Original form of the Zeiss-Nordenson retinal camera. Note the Rollex® back (not made by Zeiss) and the double-cable releases without any internal synchronization.

be wound back on itself, as use of the Rollex® back necessitated. Eight exposures per roll enables the film to be completed and processed more rapidly.

In an earlier article,[3] use of an Argus® camera back was reported. This type of camera back entails employing a 35-mm. film, with either 20 or 36 exposures per roll. In some instances, in which the total number of fundus pictures taken over a

2. By Mr. Walter G. Kramer, 209-254 Whitehall Terrace, Queens Village, Long Island, N. Y.

3. Chace, R. R., and Lafayette, J. H.: A Modified Film Carrier for the Zeiss-Nordenson Fundus Camera, Arch. Ophth. **43**:910 (May) 1950.

period of an entire week may not be very many, the delay necessitated in waiting for an entire roll of 20 or 26 exposures to be used up may prove somewhat undesirable.

In adapting the Bantam back, however, the plane of the film will no longer coincide with the original film plane. A compensating adjustment must, therefore, be made in the ocular of the camera by extending the eyepiece until the plane of focus and the plane of the film will be identical and will yield pictures in proper focus. This modified film holder has been in operation on a number of cameras for more than a year, including two models which I have had regularly in use.

MODIFICATION OF THE CABLE-RELEASE MECHANISM

The several types of the Zeiss-Nordenson camera employ various cable releases required for synchronization of the steps necessary in making an exposure, i. e., raising of the focusing mirror; release of the "compur" or mechanical shutter, and transporting of the focusing filter in the shutter leaves to allow full intensity of illumination to pass through the lens for the full duration of the exposure.

Most of the original synchronizing mechanisms are far from foolproof, errors arising from failure of the mirror to rise at the proper moment, to rise to full height, or to rise at all. Thus, a part, or, at times, nearly all of the aperture through which the light must pass to the film to produce an image, is cut off. When the aperture is thus cut off, only a partial picture is registered, or sometimes the film remains blank.

In nearly all models (Fig. 1), the double-cable releases required for the above procedures are operated by means of a hand plunger, which at times fails to keep the two cable releases taut, thus permitting them to "buckle" and loosen the tension, which is necessary to keep them in proper functioning condition. Synchronization of this type of plunger to guarantee that the flash of the exposure does not occur before or after raising of the mirror cannot be easily adjusted and checked, or kept readily in synchronization for very long.

A new type of single-cable-release mechanism, operated by a piston-like device mounted near the film holder (Fig. 2) has been installed [2] on a number of the Zeiss-Nordenson fundus cameras. The advantage of this mechanism lies chiefly in that it allows instantaneous and foolproof adjustment of the synchronization by the photographer. The cable release is mounted in vertical position on the camera, permitting it to hang straight and to be used in a manner that retains its tension and effectiveness.

With this modified cable-release mechanism, an exposure can be made only when the mirror has been completely raised, since the shutter of the camera will open for an exposure only when the mirror is in its highest position, permitting the full aperture of light to pass through.

MODIFICATION OF THE STEREOSCOPIC MODEL

The stereoscopic, binocular model of the Zeiss-Nordenson camera can be readily converted for use as a monocular, monoscopic instrument for obtaining single-frame exposures. Without interfering with the stereoscopic operation of the camera, a regular Rollex back can be mounted (Fig. 3)[2] into one of the stereoscopic sheet-film holders regularly supplied with this model. This enables use of the Bantam-size

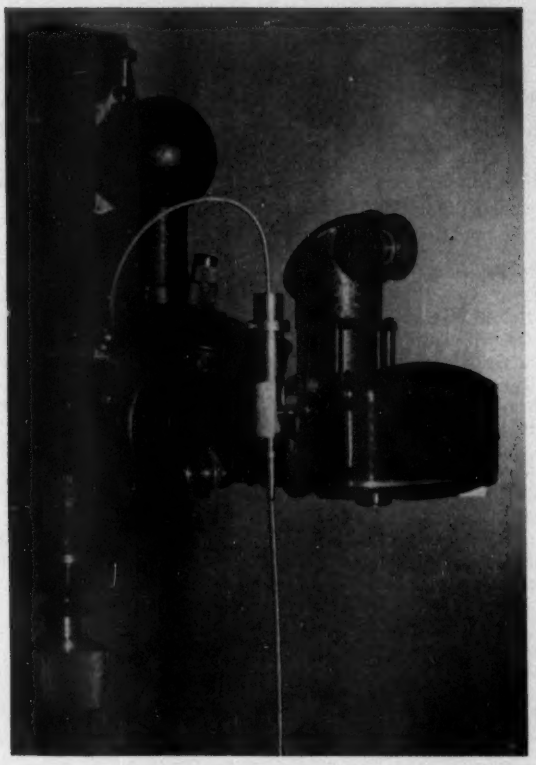

Fig. 2.—Kramer modification of Zeiss-Nordenson retinal camera. Double-cable releases have been replaced by single, continuous cable release with readily adjustable internal synchronization.

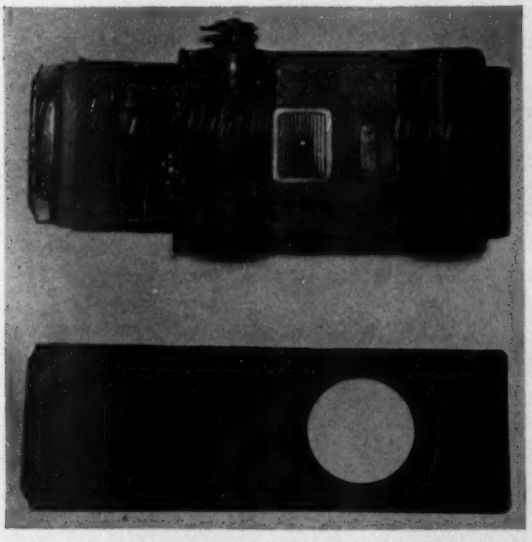

Fig. 3.—Above, Rollex® back mounted onto double-size stereo film holder to permit single exposures to be made on stereo model of Zeiss-Nordenson retinal camera. Below, slide and mask for film holder, shown above.

Kodachrome® film. The roll-film back for single exposures and the double-film holders for stereoscopic pictures can be used interchangeably, permitting both types of records to be made on the same patient, if so desired.

The modified roll-film holder is mounted in such a fashion as to enable focusing to be done through the left-hand ocular, which has cross-hairs and is adjustable to the vision of the operator.

207 E. 15th St. (3).

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Clinical Notes

A MODIFIED CROSS CYLINDER

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SINCE the advent of Jackson's cross cylinder in 1887, many modifications have been suggested and used. Among these have been a rotating cross cylinder for use in a trial frame, by Hornbogen [1]; a cross cylinder with additional markings for

Fig. 1.—Author's modification of the Jackson cross cylinder. Etched white lines and nibs form alignment aids.

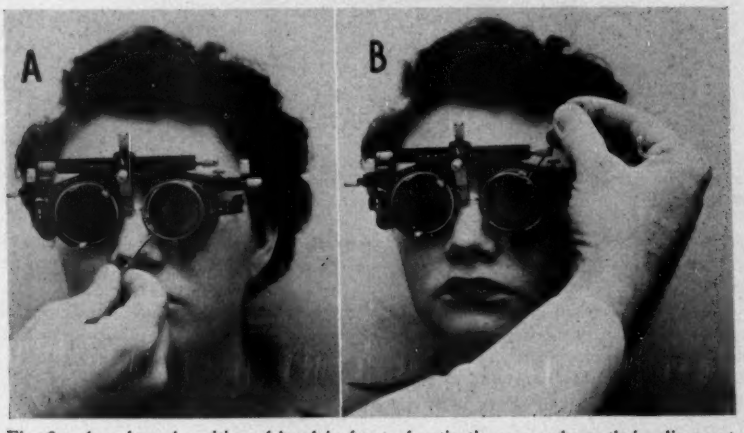


Fig. 2.—*A*, awkward position of hand in front of patient's nose and mouth in alignment of ordinary cross cylinder.

B, alternate awkward position above eye. In this position, cross cylinder is difficult to hold steady and to twirl expertly.

more accurate placement, by Mills [2]; a rotating cross cylinder in a handle, by Tree [3]; a self-setting cross cylinder, by Pascal, and others. Some of these are somewhat cumbersome, and one or two others are expensive to produce.

1. Hornbogen, D. P.: Rotating Cross Cylinder, Am. J. Ophth. **16**:902, 1933.
2. Mills, C. K.: Cross Cylinder with Additional Markings for Accurate Placement, Am. J. Ophth. **20**:408, 1937.
3. Tree, M.: A Rotating Cross Cylinder, Brit. J. Ophth. **23**:632, 1939.

The need for my own modification (Fig. 1) was suggested by the awkward position of the examiner's hand and arm which is necessary in testing for the axis of astigmatism. This depends, of course, on the axis of the trial cylinder. The most awkward positions seem to be required when the astigmatic axis is being tested near 45 degrees in the left eye and 135 degrees in the right eye. In these positions, either the hand is in front of the patient's mouth, as illustrated (Fig. 2*A*), or is in a most uncomfortable position above the eye (Fig. 2*B*).

With my modification, the additional etched white marks and little nibs on the cross cylinder are arranged so that the handle is perpendicular to an imaginary

Fig. 3.—With white lines and nibs on modified cross cylinder aligned with axis marks on trial cylinder (about 45 degrees in this case), the hand and arm are in a free and comfortable position.

line running through them, thus rendering it easy to align the cross cylinder with the white marks on the trial cylinder, while the arm and hand are in a comfortable position.

With the standard cross cylinder used at the difficult positions mentioned, the examiner usually tests with the hand before the patient's nose and mouth, a position which, for obvious reasons, is objectionable. Not the least of these objections is getting lipstick on the hand and then on the clothes or face.

The modification can be made at very small cost by any optician.

1765 Sherman Street.

A MODIFIED STRABISMUS MUSCLE FORCEPS

COLONEL J. H. KING Jr.
MEDICAL CORPS, UNITED STATES ARMY
AND
CAPTAIN R. L. FORREST
MEDICAL CORPS, UNITED STATES AIR FORCE

TWO OF the prime requisites of successful extraocular muscle surgery are consistent results and minimum danger of damage to the eye. The Jameson and Prince recession forceps have been modified to aid in attainment of these objectives (Fig. 1).

Fig. 1.—Modified Jameson recession forceps. Photography Accession No. TR 615 B.

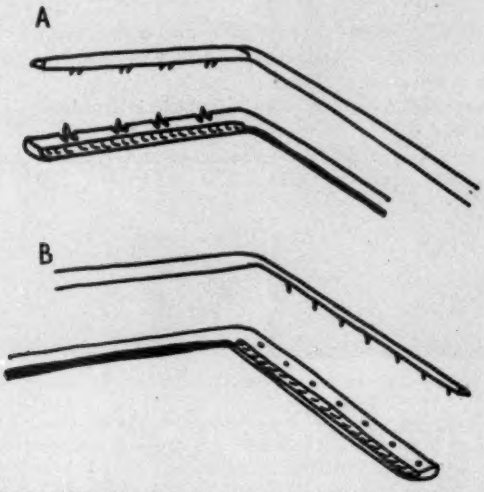


Fig. 2.—*A*, shelf modification of Prince forceps; *B*, shelf modification of Jameson forceps. Photography Accession Nos. TR 615 and 615 A.

It is difficult to obtain a consistently uniform short muscle stump when scissors are used to sever a muscle along a muscle hook or recession forceps. The ideal instrument with which to cut the muscle would be a scalpel were it not for the danger to the eye. The modified instrument [1] presented here allows the use of a

Eye Section, Tripler Army Hospital, Honolulu, T.H. (Captain Forrest).

1. Manufactured by Storz Instrument Co., St. Louis 10.

sharp knife, the cutting being done against the metal of the instrument. The lower lip of the instrument protrudes about 1 mm. beyond the upper lip on the handle side. In this narrow shelf is ground a groove, which holds the knife blade in position as the muscle is sectioned (Fig. 2*A* and *B*).

The forceps is placed on the muscle, and the scalpel blade is used to produce a clean cut against the underlying shelf, leaving a muscle stump of consistent size, without danger of a perforated globe (Fig. 3). The advantages of the instrument are therefore these:

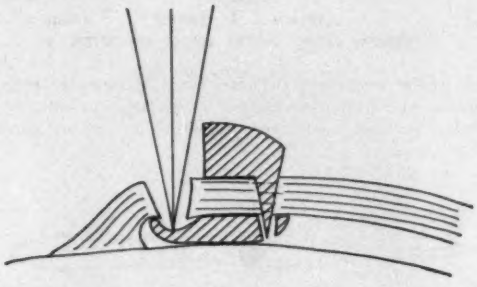


Fig. 3.—Scalpel sectioning muscle against underlying shelf of modified forceps. Photography Accession No. TR 615 C.

1. The shelf acts as a protection to the globe during the severance of the muscle.

2. A sharp scalpel or sharp-pointed scissors may be used to section the muscle against the groove in the shelf.

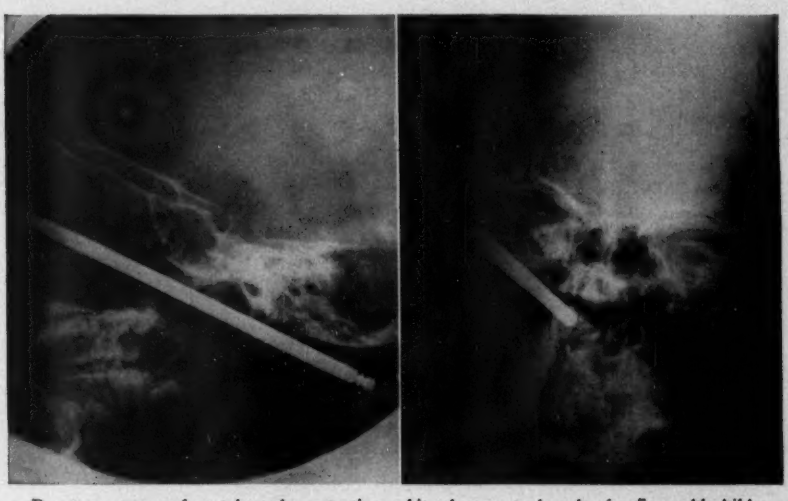
3. A clean, even muscle stump remains which is consistently about 1 mm. in length.

4. More accurate postoperative results are possible because of this standardized technique.

Registry of Interesting Cases

FOREIGN BODY (CURTAIN ROD) PENETRATING ORBIT, PHARYNX, AND NECK, WITH COMPLETE RECOVERY

C. W., a 7-yr.-old child, fell forward on a solid brass curtain rod that he had been carrying in his hand. The rod was ¼ in. (6.5 mm.) in diameter and 20 in. (50.8 cm.) in length. When the child got up, the rod had all but disappeared through a wound in the left lower lid just above the orbital margin. He was promptly sent to the hospital, where he showed no ill effects other than the wound to the orbit. Examination showed the curtain rod protruding under the left eye, the globe having been pushed upward slightly. The pupil reacted normally, and, except for some limitation in downward gaze, the eye appeared unharmed. The patient was able to



Roentgenograms of curtain rod penetrating orbit, pharynx and neck of a 7-yr.-old child.

count fingers readily with this eye. The other end of the curtain rod was found to be presenting under the skin of the neck at the left side of the atlas. The depth of penetration was 15.5 cm. Roentgenograms showed the rod penetrating the orbit, the oral pharynx, the posterior pharyngeal wall and past the atlas.

With the patient under ether anesthesia, the skin of the neck overlying the posterior tip of the rod was incised. The tip was grasped and the rod carefully extracted manually with countertraction against the head. Removal of the rod was accomplished without incident, though a considerable amount of traction was required. No suturing was done. The point of penetration was left wide open. A sulfadiazine ophthalmic ointment was instilled in the eye, and a loose dressing was applied.

The child was given tetanus and gas gangrene antitoxins. Treatment was started with penicillin, 300,000 units every eight hours, and streptomycin, 0.5 gm. every six hours. The following morning his temperature was 100.4 F. rectally, but 48 hr. later it was normal and remained

normal thereafter. Moderate ecchymosis of the orbit was present at that time, and there developed some limitation of motion in the jaw and paresis (incomplete) of the left facial nerve. This subsided, and the patient was discharged as recovered on the 10th postoperative day, with only slight discoloration of the skin around the site of the penetrating wound.

One month after operation the child was examined and found to be perfectly normal. Vision was 20/15 in each eye; ocular muscle balance was normal; the ocular media were clear, and the fundi were normal. Hearing was not impaired, and the pharynx was normal. There was no limitation of motion in the facial muscles, in the mandible, or in the cervical muscles. For the past year he has been seen occasionally and has been found to suffer no ill effects from this incident. Recovery has been complete, without evidence of permanent injury.

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Annual Reviews

PHARMACOLOGY AND TOXICOLOGY

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ANTIBIOTICS AND CHEMOTHERAPY

NUMEROUS reports have been made in the literature during the past year concerning the toxicity, the tolerance, the penetration, and the effectiveness of antibiotics.[1-10] Many new antibiotics have been introduced,[1a-f] most promising among which is viomycin.[1c,d]

From the Department of Ophthalmology, University of Pennsylvania School of Medicine, and the Wills Hospital.

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From the new data made available during the past year [1-10] the summary tables that were prepared for last year's review [1g] can be brought up to date (Tables 1 to 7).

Selection of Antibiotic.—According to Bellows,[1h] the two main principles in therapy are, first, that the organism causing the infection must be sensitive to the antibiotic chosen if treatment is to be successful,[1i,j] and, second, an effective concentration of the chosen agent must reach the site of infection and come in contact with the responsible organism. Whenever possible, one should be guided by culture and sensitivity studies as to the proper antibiotic to be used. Table 7 lists the organisms which may be responsible for infection and the antibiotic of choice. The strains of bacteria vary in susceptibility; therefore, one cannot always predict for any one particular strain. For example, some strains of Pseudomonas are more

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TABLE 1.—*Penetration into Aqueous Humor * After Instillation into the Cul-de-Sac*

Drug	Normal Cornea	Abraded Cornea
Sulfanilamide	+	+++
Sulfadiazine sodium, 10%	+	+++
Sulfamethazine sodium, 10%	++	+++
Sulfamerazine sodium, 10%	+	+++
Sulfacetamide sodium, 10%	+	+++
Penicillin sodium, 250-2,000 units/cc.	±	++
Bacitracin, 500-1,000 units/cc.	±	++
Streptomycin hydrochloride, 5000 γ/cc.	±	++
Aureomycin borate hydrochloride, 0.5%	−	++
Chloramphenicol, 0.25%	+	++
Neomycin, 0.25%	±	++
Terramycin, 0.5%	−	++
Polymyxin, 0.5%	±	++

* − indicates none; ±, poor; +, fair; ++, good; +++, very good.

TABLE 2.—*Intraocular Penetration in Normal Rabbit Eye After Intravenous Administration*

	Aqueous Humor	Vitreous Humor	Cornea	Sclera	Anterior Uvea	Posterior Uvea	Ocular Muscle	Conjunctiva	Optic Nerve	Lens
Penicillin										
4,000 units/kg.	±	−	−	−	−	−	±	+	−	−
25,000-100,000 units/kg.	++	±	+	+	+	±	+	++	+	−
Streptomycin										
10,000 γ/kg.	+	−	−	+	±	−	+	+	−	−
100,000 γ/kg.	++	+	+	+	++	+	+	++	+	−
Aureomycin										
20,000 γ/kg.	+	±	++	++	++	++	..	++	..	−
Chloramphenicol										
50,000 γ/kg.	++	+	+	+	++	+	+	++	±	−
100,000 γ/kg.	++	++	++	++	++	+	+	++	+	−
Terramycin										
50,000 γ/kg.	++	−	+	+	+	−	+	+	−	−

TABLE 3.—*Administration of Antibiotics and Chemotherapeutic Agents in Ocular Infections*

Solutions for Local Use

Drug	Concentration
Penicillin	1,000-10,000 units/cc.
Streptomycin; dihydrostreptomycin	5,000 γ/cc.
Bacitracin	1,000 units/cc.
Aureomycin	5 mg./cc.
Chloramphenicol (chloromycetin®)	2.5 mg./cc.
Neomycin	2.5 mg./cc.
Polymyxin	5 mg./cc.
Terramycin	5 mg./cc.
Sulfacetimide sodium	0.3 gm./cc.
Sulfamylon®	0.01 gm./cc.
Sulfadiazine sodium	0.1 gm./cc.
Gantrisin® *	43 mg./cc.
Sodium propionate ("propion")	0.05 gm./cc.

Ointments

Penicillin	1,000 to 50,000 units/gm. of ointment vehicle (higher concentrations may be used with crystalline penicillin)
Streptomycin-dihydrostreptomycin	5,000 to 10,000 γ/gm. of vehicle
Bacitracin	500 to 1,000 units/gm. of vehicle
Aureomycin	5 mg.+/gm. of vehicle
Chloramphenicol	2.5 mg.+/gm. of vehicle
Neomycin	2.5 mg./gm. of vehicle
Polymyxin	5 mg./gm. of vehicle
Terramycin	5 mg./gm. of vehicle
Sulfadiazine	0.05 gm./gm. of vehicle
Sulfacetimide sodium	0.1 gm./gm. of vehicle

Solution for Iontophoresis

As above; usually cathode pole on corneal electrode; 3 ma. for 2 to 3 min.

Subconjunctival Injection

Penicillin	50,000 units/0.5 cc. water or 0.25 cc. of 1:1,000 epinephrine hydrochloride and 0.25 cc. of water (can use 0.25 cc. of 2% procaine hydrochloride)
Crystalline penicillin	1,000,000 units/0.25 cc. of 1:1,000 epinephrine hydrochloride + 0.75 cc. water
Streptomycin; dihydrostreptomycin	10,000-20,000 γ/0.5 cc. water, or as above
Aureomycin	2.5 mg./0.5 cc. water
Chloramphenicol	1.2 mg./0.5 cc. water, or 25 mg./0.5 cc. of propylene glycol
Neomycin	1.2 mg./0.5 cc. of water
Polymyxin	2.5 mg./0.5 cc. of water
Terramycin	2.5 mg./0.5 cc. of water
Paraaminosalicylic acid	100-250 mg./0.5 cc. of water

* 3,4-dimethyl-5-sulfanilamidoisoxazole.

susceptible to streptomycin than to polymyxin,[1k] although in the majority of instances in which tests were made by Wiggins [11] polymyxin was the most successful agent tested against this organism. So it will be seen that in not all instances will the selected antibiotic be successful on the basis of sensitivity studies. The best test is clinical trial. If adequate therapy shows no evidence of response within 72 hr., another antibiotic should be chosen.

TABLE 4.—*Penetration into Aqueous and Vitreous Humor After Oral Administration*

	Aqueous Humor	Vitreous Humor
Aureomycin		
50 mg./kg.	−	−
Chloramphenicol		
100 mg./kg.	++	+
Terramycin		
100 mg./kg.	−	−

TABLE 5.—*Dosage of Antibiotics for Systemic Administration*

Drug	Concentration	Method
Penicillin	(1) 50,000-100,000 units every 3 hr., aqueous solution	Intramuscular
	(2) 200,000 units every 12 hr., crystalline in aqueous solution	Intramuscular
	(3) 300,000 units every 12 hr., oily or aqueous solution	Intramuscular
	(4) 300,000 units, procaine complex in oil with 2% aluminum monostearate every 48 hr.	Intramuscular
	(5) 5,000,000 units daily	Continuous intramuscular or intravenous drip
	(6) 100,000 units every 3 hr.	Oral
Streptomycin	(1) 1 to 2 gm. daily; divided doses	Intramuscular
	(2) 1 to 2 gm. every third day	
Aureomycin	(1) 25 to 50 mg./kg. body weight, initial dose 50 mg./kg. body weight—daily dose, subsequently divided into 4 doses (approximately 1.0 to 1.5 gm. stat. and 0.5 gm. every 6 hr. thereafter)	Oral
	(2) 0.5 mg./kg., initial dose 15 mg./kg. in divided daily doses, usually every 3 hr.	Intravenous
Chloramphenicol	(1) 60 mg./kg. body weight, initial dose 30-60 mg./kg. body weight, maintenance dose daily Average dose 3 gm. stat., 0.5 gm. every 4 hr. subsequently	Oral
	(2) 15 mg./kg. body weight every 6 hr., dissolved in acetyldimethylamine, 1% solution in 5% dextrose	Intravenous
Terramycin	(1) 25-50 mg./kg. body weight, initial dose 50 mg./kg. body weight—daily dose, subsequently divided into 4 doses (approximately 1.0 to 1.5 gm. stat., and 0.5 gm. every 6 hr. thereafter)	Oral
Viomycin	30-100 mg./kg. body weight of viomycin sulfate, 10% solution	Intramuscularly Also may be given subcutaneously and intravenously

TABLE 6.—*Doses Tolerated by Intraocular Injections*

Anterior chamber or vitreous chamber	Penicillin	1,000-5,000 units/cc. of water
	Streptomycin; dihydrostreptomycin	1,000 γ/0.1 cc. of water
	Bacitracin	10-100 units/0.1 cc. of water
	Aureomycin	50 γ/0.1 cc. of water
	Chloramphenicol	250 γ/0.1 cc. of water
	Terramycin	250 γ/0.1 cc. of water
	Neomycin	250 γ/0.1 cc. of water

Despite the advent of antibiotics which may partially replace it, demand for penicillin has remained high.[2c] It is still, in many ways, the least expensive of the antibiotics for systemic therapy. Perhaps the most noteworthy trend in penicillin therapy has been the adoption of sodium or procaine penicillin G preparations in the treatment of virtually all infections caused by penicillin-sensitive organisms.

Three forms of penicillin G are now available. In addition, a form of procaine penicillin G with crystalline potassium penicillin G is also available.[m-t] This is especially useful if high tissue concentrations are desired immediately. This preparation has disadvantages, however, in that it is relatively unstable once the diluent has been added. It is considerably more expensive than the plain procaine peni-

TABLE 7.—*Susceptibility of Organisms to Various Antibiotics*

Organism	Antibiotic Recommended
Gram-positive cocci	Penicillin
Penicillin-resistant strains	1. Aureomycin or terramycin 2. Bacitracin (local)
Gram-negative cocci	
Gonococcus	1. Penicillin 2. Aureomycin, chloramphenicol, or terramycin 3. Bacitracin (local)
Meningococcus	1. Sulfadiazine and sulfamerazine 2. Bacitracin (local)
Gram-positive rods	
Bacillus anthracis	1. Penicillin
Clostridia	2. Sulfadiazine and sulfamerazine Aureomycin, chloramphenicol, or terramycin (antibacterial therapy always secondary to antitoxin therapy)
Gram-negative rods	
Coli aerogenes group	1. Streptomycin, chloramphenicol, aureomycin, or terramycin
Typhoid-Salmonella group	1. Chloramphenicol 2. Aureomycin
Brucella	1. Chloramphenicol, aureomycin, or terramycin
Shigella	1. Sulfonamides, chloramphenicol, aureomycin, or terramycin
Hemophilus influenzae	1. Streptomycin, aureomycin, chloramphenicol, or terramycin
Hemophilus pertussis	1. Chloramphenicol 2. Aureomycin or terramycin
Proteus vulgaris	1. Streptomycin, chloramphenicol, or neomycin
Pseudomonas aeruginosa	1. Polymyxin (but nephrotoxic), streptomycin, chloramphenicol, aureomycin, sulfonamides—all occasionally fail
Spirochetes	
Syphilis	1. Penicillin
Yaws	2. Aureomycin or chloramphenicol
Relapsing fever	3. Bacitracin (nephrotoxic)
Spirochetal jaundice	
Mycobacteria	
Tubercle bacillus	1. Streptomycin or dihydrostreptomycin in combination with paraaminosalicylic acid, thiazolsulfone,* or thiosemicarbazone 2. Viomycin
Rickettsias	
Typhus	Chloramphenicol, aureomycin, or terramycin, all superior to paraaminobenzoic acid
Murine typhus	
Tsutsugamushi fever (scrub typhus)	
Rocky Mountain spotted fever	
Q fever	
Viruses	
Psittacosis	Penicillin, chloramphenicol, aureomycin
Lymphogranuloma venereum	Aureomycin, chloramphenicol, or terramycin
Trachoma	Sulfonamides, penicillin, chloramphenicol, aureomycin
Inclusion blennorrhea	Sulfonamides
Atypical pneumonia	Chloramphenicol or aureomycin

* Promizole.®

cillin G; yet it has certain advantages in cases of ocular infections in which high blood concentrations are desired in order to obtain more adequate intraocular concentrations.

Aluminum monostearate preparations impede absorption so effectively that small amounts of penicillin may be detected in the blood for as long as four days after a single injection of 300,000 units. However, such doses do not guarantee high or adequate intraocular concentrations.

Tuberculosis remains the principal disease for which streptomycin therapy is indicated.[11]

Definition.—Vuillemin, in 1889, called attention to the terms "antibiotic" and "antibiosis." These were used in the sense of absolute opposition of one organism to another. In 1899 Ward defined antibiosis as the converse of symbiosis, as an association of organisms whereby one injures another, as had been exemplified by many parasites. In 1951 Waksman [2u] defined an antibiotic as a chemical substance, produced by a micro-organism, which has the capacity to inhibit the growth of, and even destroy, bacteria and other micro-organisms in dilute solutions.

Bacterial Resistance.—In the few years in which antibiotics have been available on such large scale, it has become evident that organisms develop resistance to antibiotics if they are in contact with the antibiotic for a sufficiently long time.[2v-x] It has been noted that some strains of Staphylococcus obtained from patients with penicillin therapy may vary widely in their sensitivity to penicillin, and that resistant strains are very frequently encountered.[2a]

It has been known for some time that organisms have the ability to produce an enzyme which will inactivate penicillin. This has been called penicillinase.[12] Strains of bacteria resistant to various sulfonamide drugs, as well as strains resistant to penicillin, can readily be obtained by use of mediums containing increasingly higher concentrations of the respective chemicals. Resistance of staphylococci to certain concentrations of penicillin may not be induced by the action of penicillin on bacteria, but may arise independently by mutation. In any large population of the strain of Staphylococcus there are individual organisms resistant to low concentrations of penicillin. If this population is exposed to the action of such concentrations of penicillin, nonresistant organisms are eliminated, and the resistant ones survive. Thus, penicillin acts as a selective agent, which suppresses nonresistant bacteria.

Staphylococci, as well as other organisms, may develop a resistance to penicillin which is not permanent. This is not associated with the release of penicillinase. The permanent type of penicillin resistance, however, is associated with the release of penicillinase. Many such resistant strains of staphylococci can result from inadequate therapy in patients with initially penicillin-sensitive strains. This biologic feature of resistance to penicillin is of extreme importance in the epidemiology of staphylococcic infections and can be correlated with the increasing incidence of therapeutic failures of penicillin.

Penicillin is now frequently and widely administered, and as a result penicillin-resistant strains will appear more diffusely through the population. The carrier rate of these resistant strains will increase, and the incidence of penicillin-resistant staphylococcic infection will rise. Persons who have never received penicillin will become infected with penicillin-resistant strains of Staphylococcus. The appearance of such highly resistant strains is definitely related to the widespread use of the antibiotic. It is recommended that, in order to prevent drug-resistant micro-organisms from developing, one should consider the employment of newer antibiotics, or

11. Hager.[1u] De Jean, Cazabon, and Gassenc.[1v] Missirolli.[1w] Bietti.[1x] Germaine and Nako.[1y] Donegan.[1z] Dunphy.[1a'] Heinsius.[2a] Peiqer.[2b] Kirby.[2c] Wallner, Turner and others.[2d] Rees and Robson.[2e,f] Hinshaw.[2g] Jones, Stearns, and Himmelstein.[2h] Weitzman, Cayley, and Wingfield.[2i] Thomas.[2j] Alvarez-Alvarez.[2k] Woods, Wood, and Naquin.[2l, m] Sykowski.[2n] Appelmans, and others.[2o] Alvarez.[2p] Missirolli.[2q] Das Gupta.[2r] Pritikin, Duchon, and Farmer.[2s] Parisi.[2t]

12. Czekalowski.[2x] Garrod.[3b] Editorial.[3c]

perhaps the various combinations of them with penicillin. At the same time, there must be a continued search for other antibiotics which may be used to overcome some of the problems now associated with antibiotic therapy.

Strains rapidly develop resistance to streptomycin.[13] This is particularly true of gram-negative organisms and of the tubercle bacillus.

Resistance has developed slowly to chloramphenicol, aureomycin, and terramycin,[14] but resistance has been reported as occurring to neomycin [3n-p] and to viomycin.[15]

It has been the experience of most investigators that in order to avoid organismal resistance prompt therapy with adequate dosage is the best means. It has actually been demonstrated that a low dose of chloramphenicol will stimulate bacterial growth; this occurs also with other antibiotics.[3y]

Resistance to penicillin and streptomycin appears to occur particularly when there are anatomic obstacles to clearing up the infection, where the antibiotic may not reach the organism in sufficient concentration, as in ocular tissues.[2n]

According to Garrod,[3b] bacteria react in four ways to chemotherapeutic and antibiotic agents. 1. There may be suppression of the organism, in which the organism actually dies or the antibiotic simply inhibits the growth of the organism. 2. The organism may habituate itself to the antibiotic, in which case it acquires resistance. 3. The organism may become dependent on the antibiotic for nutrition; that is, it becomes dependent on a substance which is normally lethal to it. It has been demonstrated with streptomycin therapy that the patient may fail to improve until the streptomycin has been withdrawn. Without streptomycin the organisms are no longer able to multiply. 4. Some bacteria may actually be stimulated in growth by the antibiotic.

Organisms acquire resistance slowly to aureomycin, chloramphenicol, and terramycin. The resistance is moderate in degree and is not necessarily permanent. When organisms are resistant to terramycin, they also become resistant to aureomycin and chloramphenicol.[3a] The ability of antibiotics, such as penicillin, apparently to stimulate the growth of other bacteria, which are not sensitive to it in the first place, has been noted in ophthalmology.[4a] When eyes were treated locally with penicillin, it was found that the Proteus organism grew more rapidly than when penicillin solutions were absent, suggesting that penicillin in some way was facilitating or stimulating the growth of the Proteus organism. This may be because the penicillin killed off or inhibited the growth of the other bacteria, so that the local pH was altered favorably for the growth of Proteus. Possibly penicillin, in inhibiting the growth of other organisms, made possible more nutrition to be available for the Proteus organism, or penicillin may have been depleting some material from the tissues which was inhibiting the growth of the Proteus organism. Perhaps the bacteria which were inhibited in growth by penicillin were liberating a substance which was like an antibiotic and inhibited the growth of the Proteus organism. By killing off these bacteria in the flora of the conjunctival cul-de-sac,

13. McLean.[2y] Keefer.[2s] Spink.[3a] Editorial.[3c] James, and others.[3d] Temple, and others.[3e] Spain and Childress.[3f] Hamburger, and others.[3g] Adcock, and others.[3h] Hoggarth and Martin.[3j] Croshaw and Dickenson.[3k] Francis, Spinks, and Stewart.[3l]

14. Hirsch.[1d] Keefer.[2s] Spink.[3a] Delliteri and Frede.[3m]

15. Werner, Tompsett, and McDermott.[1c] P'an, Halley, and others.[3q] Karlson and Gainer.[3r] Steenken and Wolensky.[3s] Youmans and Youmans.[3t] Hobb, and others.[3u] Ehrlich, and others.[3v] Bartz, and others.[3w] Finlay, and others.[3x]

these organisms were no longer available to produce the material which inhibited the growth of the Proteus.

Perhaps a similar mechanism is responsible for the more rapid growth of Candida albicans in the presence of aureomycin, terramycin, chloramphenicol, and penicillin.[4b]

Combination of Antibiotics.—Theoretically, there are many obvious advantages to the use of combinations of antibiotics.[16] For example, in treating infections due to mixed bacteria, i. e., gram-positive or gram-negative organisms, penicillin can be used to attack the gram-positive organisms and streptomycin to attack the gram-negative ones. This combination has actually been shown to be effective against such infections. But aureomycin alone does almost as well. Another theoretical advantage would be that the second antibiotic would prevent superinfection. For example, staphylococcic infections may develop with prolonged streptomycin therapy, or staphylococcic organisms resistant to penicillin may develop after prolonged penicillin therapy. Cases of staphylococcic dysentery have been reported to follow prolonged penicillin therapy, and cases of resistant B. coli have been described as growing in the gastrointestinal tract of tuberculous patients treated with streptomycin for long periods. Another theoretical advantage is that smaller doses of each of the two antibiotics may prevent toxic reactions from either. The combination may delay the appearance of resistant organisms, such as has been demonstrated to occur with streptomycin-paraaminosalicylic-acid combinations. Another possibility is that true synergism may result, such as has been suggested for the combination of aureomycin and streptomycin for the Brucella organism,[4m] and of penicillin and bacitracin against the Treponema pallidum.[4d] However, a word of warning should be said against the use of combinations which have not been shown to be better in any way than either drug alone. For example, Jawetz and his associates [4n] have demonstrated a definite antagonistic effect between chloramphenicol and penicillin—in vitro with both gram-positive and gram-negative organisms and in vivo in a streptococcic infection in mice. The antagonism of the two drugs extends over wide ranges of concentration of each drug but is limited by the degree of antimicrobial activity of the drug. The phenomenon is observed in vivo when the drugs are given at different sites, as either single or multiple injections. However, antagonism occurs only if chloramphenicol is given prior to or simultaneously with penicillin, and not if penicillin is administered first. Drugs synergistic with penicillin, for example, streptomycin or bacitracin, can overcome the antagonism between penicillin and chloramphenicol. Evidence indicates that the phenomenon is not one of mutual antagonism of the two drugs, but is an interference of chloramphenicol with the early bactericidal or therapeutic effect of penicillin. It is probably not a physical or chemical interaction of the two drugs; rather, chloramphenicol modifies the characteristics of the bacterial population so as to make it less susceptible to penicillin action.[4n]

16. Long.[1p] Long, Bliss, and Schoenback.[1q] Dunphy.[1a'] Kirby.[2c] Rees and Robson.[2o] Alvarez.[2p] Keefer.[2s] Temple, and others.[2e] Spain and Childress.[3f] Adcock, Fidler, Meier, and Owen.[3h] Croshaw and Dickenson.[3k] Francis, Spinks, and Stewart.[3l] Boger and Pitts.[4c] Johnson and Meleny.[4d] Jefferis, Willcox, and McElligott.[4e] Jonwicke.[4f] Steenken and Wolnsky.[4g] Tolentino.[4h] Bonavolanta and de Berardinas.[4i] Dowling.[4j] Paine.[4k] Cannon, Leopold, and Shope.[4l]

Spicer [4o] has demonstrated in vitro that this property of chloramphenicol to interfere with the action of penicillin is also shared by aureomycin against many strains of organisms. This effect of antibiotics in combination (1) to be additive, (2) to be synergistic, (3) to have no effect, or (4) to interfere with the action of each other can be demonstrated to differ for particular strains of the same organism. Therefore, one cannot always predict for any one organism exactly what the combination will do. Nor does it follow that by in-vitro testing one can be certain that actual clinical trial will parallel the in-vitro results.

Considerable evidence is appearing in ophthalmologic and in the general literature confirming the advantages of the combination of streptomycin and *p*-aminosalicylic acid, or of streptomycin and diacetozone in the therapy of tuberculosis.[17]

Rees and Robson [2e] made various attempts to enhance the action of streptomycin, either by combining it with other drugs, such as potassium iodide or *p*-aminosalicylic acid, or by making a compound of streptomycin and *p*-aminosalicylic acid. In their investigation, Rees and Robson [2f] used a method by which tuberculous abscesses are produced in the rabbit and the mouse cornea. Their results show that potassium iodide had an enhancing effect on the action of streptomycin against tuberculous lesions of the cornea, but that potassium iodide had no enhancing effect on the action of paraaminosalicylic acid. Combined therapy with streptomycin and *p*-aminosalicylic acid was superior to the use of the single streptomycin-*p*-aminosalicylate compound.

Toxicity.—There have been many instances of sensitivity developing to the antibiotic, practicaliy all the antibiotics having been reported as producing some form of sensitivity reaction.[18] Penicillin, which has been more widely used than any other antibiotic, has been most thoroughly studied from this standpoint. Sensitivity to antibiotics usually does not produce a demonstrable antibody.[2z] It will take the form of contact dermatitis, serum sickness, occasionally severe angioneurotic edema, or even, more rarely, anaphylactic shock. Such reactions occur most frequently in patients who have had several courses of therapy with the antibiotic. Urticaria may develop, which may or may not disappear with continuous use of the drug. Skin tests are unreliable in predicting in which patient such sensitivities to antibiotics will develop.

The antihistaminics may or may not be useful in controlling the reactions. The most frequently encountered manifestation of sensitization is that following local application of either drops or ointments.

Aqueous preparations of penicillin give fewer reactions than the absorption-prolonging base types of penicillin, such as those containing heparin or beeswax and those containing procaine.[2d] Procaine itself may be the responsible factor in the sensitivity reaction. With penicillin, a peculiar type of sensitivity may occur; the use of this agent may light up previous Trichophyton infections.

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17. De Jean, Cazabon, and Gassenc.[1v] Missirolli.[1w] Bietti.[1x] Germaine and Nak.[1y] Donegan.[1z] Wallner, Turner, and others.[2d] Rees and Robson.[2e, f] Alvarez-Alvarez.[2k] Woods, Wood, and Naquin.[2l] Missirolli.[2q] Spain and Childress.[3f] Hoggarth and Martin.[3j] Croshaw and Dickenson.[3k] Francis, Spinks, and Stewart.[3l] Bonavolanta and de Berardinas.[4l] Salgado-Benevidas.[4p] Pejanney, Cox, and Grindall-Balchum.[4q] Editorial.[4r]

18. Werner and others.[1c] Bellows.[1h] Fried.[1r] Hager.[1u] Dunphy.[1a'] Heinsius.[2a] Kirby.[2c] Chandramolli.[4t] Weeker.[4u] Burstein.[4v] Leopold.[4w] Worthington.[4x] Peck.[4y] Gilman.[4z] Sherman.[5a] Santos-Almeida.[5b] Egan.[5c] Simon.[5d]

Contact dermatitis, having developed from penicillin, does not exclude the subsequent use of this agent, since less than 1% of affected patients will react after systemic injections of penicillin.

Once a reaction has developed to systemic penicillin, the patient may have an accelerated reaction to a second course, or no reaction at all. The time that elapses is important; the longer the interval, the less likely is the second reaction to occur.

Streptomycin produces a cutaneous reaction in about 5 to 7% of patients. Sometimes the skin will clear, although therapy has been continued, but in about 15% of persons who show the sensitivity, the rash becomes worse with continued therapy. Sometimes the cutaneous reaction is associated with fever. Eczema of the lids has been reported frequently with streptomycin, and also with aureomycin.[19]

Because of the possibility of the development of sensitivity, all antibiotics should be used with great discretion. Ophthalmologists should give considerable attention to such drugs as neomycin, polymyxin, bacitracin, and perhaps, if the results of Theodore [5e] are confirmed, to sodium propionate. The first three of these agents, because of nephrotoxicity, and ototoxicity in the case of neomycin, are less likely to be used for generalized infections by the systemic route. Other agents, such as penicillin, aureomycin, terramycin, and chloramphenicol, are preferable for systemic administration. However, all three—neomycin, bacitracin, and polymyxin—are effective antibiotics when locally employed. Bacitracin is very potent against gram-negative organisms, some of which are resistant to penicillin. Neomycin has a wider antibacterial spectrum against gram-negative and gram-positive organisms and seems to be particularly effective against some strains of Proteus. Polymyxin has a wide spectrum against gram-negative organisms and is particularly effective against many strains of Pseudomonas aeruginosa and Pseudomonas pyocyanea. These drugs, in designated concentrations, can be used locally with relatively little danger of toxicity.

In addition to hypersensitivity reactions, the antibiotics produce other toxic signs.[20] As already mentioned, bacitracin, neomycin, and polymyxin produce renal damage, and neomycin may induce deafness. Streptomycin is known to produce vestibular dysfunction; although dihydrostreptomycin was developed in an effort to reduce the incidence of vestibular dysfunction, its success does not seem to be borne out by increasing clinical experience.[5p]

Aureomycin, chloramphenicol, terramycin, and penicillin have produced lesions of mucous membranes, some of which have taken on characteristics of moniliasis.[21] Clinical infections of the pharynx, esophagus, and intestinal tract, and even pulmonary moniliasis, have developed from the use of these agents. The patient often may first complain of a burning sore tongue, mouth, and throat, or he may have pulmonary lesions, which may become rather severe. In the case of the oral lesions, the tongue is usually thickly coated, often with an overgrowth of filiform papillae,

19. Wallner, Turner, and others.[2d] Woods, Manning, and Patterson.[4b] Burstein.[4v] Worthington.[4x] Santos-Almeida.[5b] Egan.[5e] Simon.[5d]

20. Werner, Tompsett, and McDermott.[1c] Bellows.[1h] Fried.[1r] Heinsius.[2a] Peiqer.[2b] Kirby.[2c] Hinshaw.[2g] Jones, Stearns, and Himmelstein.[2h] Thomas.[2j] Duncan, Clancy, and others.[3n] Wolgamott and Duncan.[3o] P'an, Halley, Reilly, and Pekich.[3q] Dowling.[4j] Paine.[4k] Editorial.[4r] Leopold.[4w] Worthington.[4x] Peck.[4y] Haunz, Cardy, and Graham.[5f] Felder and Felder.[5g] Ross, and others.[5h] Cruickshank.[5i] Whitmer.[5j] Kagan, Krevsky, and others.[5k] Sayer, and others.[5l] Lowe.[5m] Greenwood.[5n] Finland.[5o]

21. Woods, Manning and Patterson.[4b] Zimmerman.[5q]

giving it a brown or black hairy appearance. The tongue later becomes beefy red, dry, and swollen, and very tender to palpation and to contact with the acid juices of foods. The sense of taste is greatly altered. After this exudate disappears, the buccal mucous membrane is left dry, glazed, and parched. The same phenomenon may occur in the tonsils and pharyngeal walls and may be present in intestinal mucous membrane, as well as in pulmonary mucous membrane. It may be that the use of methyl and ethyl "para-ben," as employed by Lederle Laboratories with aureomycin, may prevent the overgrowth of Candida albicans.

Sporadic reports have occurred suggesting that some of these antibiotics may produce alterations in the blood picture.[56f,r]

Schedules of Therapy.—Various schedules of therapy are listed in Tables 1 to 7. Considerable speculation has prevailed as to whether, in the use of antibiotics, it is desirable to sustain their concentration in the body at effective levels, or whether they may be given intermittently, with long periods during which the serum concentrations are below the effective threshold.[5t] It has been fairly well established that penicillin is able to exert a bactericidal effect only as long as it remains above the effective level at the locus of infection. Thus, it is theoretically necessary to maintain a maximally effective level with penicillin wherever the infection may exist. However, intermittent therapy with penicillin may be effective. The reason for this is that after penicillin has fallen below effective levels, the still-surviving bacteria do not begin to multiple immediately. They are somewhat inhibited in their growth temporarily and may succumb to the natural forces of resistance.[5s] The duration of the growth-lag period, after exposure to penicillin, varies in relation to the strain of the organism, the concentration of penicillin to which the organism has been exposed, and the duration of that exposure. In general, therefore, intermittent therapy will be effective provided the penicillin-free interval is not long enough to permit the recovery and extensive remultiplication of the surviving organisms. Those organisms which are able to survive the natural resistance of the body and are not sufficiently interfered with by penicillin will survive and multiply under such a regimen. It should also be noted that a concentration of penicillin which is sufficient to inhibit the growth of an organism is not a concentration that will necessarily kill the organism. It may require two, four, or even 10 times as great a concentration for bactericidal effect. In the case of ocular tissues, we should strive particularly for bactericidal concentrations, rather than bacteriostatic ones, as the levels we obtain in the interocular tissues and fluids are decidedly lower than those obtained in other body tissues after systemic administration of penicillin.

Ophthalmologists should strive for extremely high blood levels in order to be certain of adequate concentration in intraocular tissues and fluid. Only speculation can be applied at present to these considerations with respect to other antibiotics. With streptomycin the rate of bactericidal action increases strikingly with the concentration of the drug, whereas with penicillin there is a maximal level above which, if one increases the concentration, no further bactericidal effect is noted.[5t] It is reasonable to infer that the larger the dose of streptomycin, the higher the concentration obtained in the blood in the infected tissue, and the more rapid the bactericidal effect in that infected tissue.

Aureomycin and chloramphenicol are only slowly and slightly bactericidal in vitro, and the rate of that direct effect is only slightly increased at higher concen-

trations. The highly satisfactory clinical response obtained with these two antibiotics in infections caused by susceptible organisms, despite their slow, direct bactericidal action, suggests that with these drugs, unlike penicillin, host factors play an important role in their therapeutic effect.

There is no doubt that therapeutic levels of penicillin and other antibiotics can be obtained in the intraocular fluids and tissues by injection of the correct dose of the antibiotic subconjunctivally, by iontophoresis, and by other local measures.[22] Lepri,[5x] in an attempt to determine means of preventing rapid elimination of penicillin from the subconjunctival area, studied substances which might prolong the presence of penicillin subconjunctivally, thus maintaining high intraocular concentrations for a longer period. Various delaying substances were tried, such as penicillin associated with epinephrine hydrochloride 1 : 1,000, penicillin in pectin, penicillin procaine, and penicillin in procaine-pectin combination. He found the most effective agent for prolonging penicillin intraconjunctivally, for allowing high intraocular concentrations to be maintained for a long period of time, to be procaine penicillin and penicillin-epinephrine. In these studies, he used 100,000 units of procaine penicillin G suspended in water, and 100,000 units of penicillin in 0.5 ml. of epinephrine hydrochloride solution 1 : 1,000.

Sorsby and Unger [5y] have shown that vitreous infections can be controlled by the intraconjunctival route when 1,000,000 units of crystalline penicillin G in 1.0 cc. of water and 5 minims (0.308 cc.) of epinephrine hydrochloride solution 1 : 1,000 are used. The injections are repeated every 24 hr. for two or three days after the vitreous has completely cleared. In most instances this meant maintaining treatment for from five to seven days.

There is always the doubt, when one is trying to apply the results of penetration studies obtained in experimental animals to pathologic conditions in man, whether penetration through the human blood-aqueous barrier is in any way comparable to penetration through the blood-aqueous barrier in the experimental-animal eye. Recent studies with penetration of chloramphenicol into the experimental-animal eye have been confirmed to some extent by similar analyses on human eyes. The data reveal that when 3 gm. of chloramphenicol is administered initially, followed by 0.5 gm. every four hours, definite intraocular concentrations of the agent are found in the aqueous and vitreous humor and that these intraocular levels can be maintained on such a dosage schedule.[4w] Similar penetration levels have been shown to occur after the administration of paraaminosalicylic acid in human eyes.

De Ferrari [7y] found that when the blood of rabbits contained 11 mg. of paraaminosalicylic acid per 100 cc. the aqueous humor showed about 4 mg. of the drug per 100 cc. The value dropped, so that none was detectable after 12 hr. In the human eye, levels were detected in an eye with iridocyclitis and in one showing an incipient senile cataract after intravenous administration of 4 gm.

The experiments with chloramphenicol, showing that the drug passed across the blood-aqueous barrier of the human eye, have been confirmed also, indirectly. Williams and Dart [6a] demonstrated that chloramphenicol passed readily across the cerebrospinal fluid barrier, which does have some similarity to the blood-aqueous barrier. Saubermann [5z] analyzed the aqueous and vitreous samples from 33 human

22. Dunphy.[1a'] Appelmans, Michiels, Delfos, and van Assche.[2o] Wolgamott and Duncan.[3o] Leopold.[4w] Rohbeck.[5u] Silvan-Lopez.[5v] Blatt.[5w] Lepri.[5x] Sorsby and Unger.[5y] Saubermann.[5z]

eyes which had received penicillin subconjunctivally. Up to four hours after one subconjunctival injection of 100,000 Oxford units of penicillin in saline solution plus procaine, the vitreous was found to contain 0.5 or more unit of penicillin per cubic centimeter. The addition of epinephrine hydrochloride 1 : 1,000, as recommended by Sorsby, produced greater and more lasting penicillin concentrations in the vitreous. Saubermann [5a] also found that the eye could tolerate 100,000 Oxford units of penicillin G in 0.1 or 0.2 cc. of saline solution when injected into the anterior chamber. In his hands, this is an effective, simple, and noninjurious method of treating intraocular infections, particularly when two subconjunctival injections of penicillin, six hours apart, have not produced a decided change for the better in the course of an intraocular infection, and when one is reasonably certain that the organism is penicillin-sensitive.

Aluminum hydroxide gel ("amphojel") has been successfully employed to counteract the nausea and vomiting that may occur with aureomycin therapy, but this simultaneous administration of aluminum hydroxide gel and aureomycin produces a pronounced depression of the serum levels of this antibiotic. Aluminum hydroxide gel, basic aluminum carbonate gel (called "basaljel"), and aluminum phosphate gel (called "phosphagel"), all produce a depression of the serum levels of terramycin and aureomycin. Simultaneous ingestion of food, however, causes no significant alteration of blood levels and appears to be a more appropriate method of controlling nausea and vomiting.[6b] Various substances have been tried which interfere with the renal excretion of the antibiotics and thus increase the blood level, both in height and in duration.[23]

"Benemid" (para-[di-*n*-propylsulfanyl]-benzoic acid) appears to be the most successful of these agents to date. It is easily administered as a 0.5 gm. dose four times a day, so that a total of 2.0 gm. is used daily.

Carinamide (4′-carboxyphenylmethansulfonanalide) also has been used, but a large number of tablets must be administered, at very frequent intervals, and sodium is lost if large doses are required, so that this drug has not been received very favorably.

A daily dose of paraaminosalicylic acid, which is being used increasingly in treatment of tuberculosis, of from 8.0 to 16.0 gm. per day has been recommended. The amount of this dose is usually based on the patient's ability to tolerate paraaminosalicylic-acid medication, not on the belief that it represents the optimal dose. Some workers believe that 20 mg. a day would be desirable. Therefore, an agent capable of enhancing the plasma concentrations of paraaminosalicylic acid would be worthy of administration, although a direct relationship of the plasma concentration of paraaminosalicylic acid to its therapeutic effect has not been established. This relationship, within limits, can be anticipated.

Boger and Pitts [4c] have demonstrated that "benemid," which is Sharp & Dohme's name for para-(di-nitropropylsulfanyl)-benzoic acid, inhibits the conjugation of paraaminosalicylic acid, so that the drug is presented to the kidney in a form less rapidly excreted than are the conjugates of paraaminosalicylic acid. An adequate dose of "benemid," in combination with paraaminosalicylic acid, would be expected to result in more prolonged and higher plasma concentrations of the latter. On the basis of their observation, plasma concentrations of paraaminosalicylic acid are

23. Flippin and Boger.[1a] Boger and Pitts.[4c] Boger.[6c] Waldo and Tyson.[6d]

enhanced two to four times. Therefore, "benemid" may extend or greatly increase the efficacy of paraaminosalicylic acid in the treatment of tuberculosis.

Intermittent administration of streptomycin regimens are found to be successful in the treatment of pulmonary tuberculosis. A dose of 1 to 2 gm. is administered every three days. This can be combined with paraaminosalicylic acid, 12 gm. daily. Such therapy has been found to be equal or superior to that of the daily administration of streptomycin combined with paraaminosalicylic acid and to intermittent use of streptomycin alone. This form of therapy is thought to lower the incidence of toxicity from streptomycin and to delay the emergence of resistant strains.[3d, e] Such dosage schedules have not been thoroughly studied, nor have they been applied to ocular tuberculosis.

Unless one is prepared to evaluate this form of therapy in a large number of cases, it might be better to adhere to proved regimens in the therapy of ocular tuberculosis.

Prophylactic Therapy.—Several institutions in the country are using combinations of penicillin and streptomycin intramuscularly and locally, before operation and for a few days after, in an effort to prevent postoperative infections. No reports could be found during the past year on the merits of such therapy. Preoperative medication with terramycin, aureomycin, or chloramphenicol, each of which has wide antibacterial spectrums against gram-positive and gram-negative organisms, might be as effective as the combination of penicillin and streptomycin. However, oral administration of terramycin, aureomycin, or chloramphenicol is sometimes associated with nausea, retching, and even vomiting; and this would be hazardous after intraocular surgery. Therefore, such prophylactic therapy is not to be recommended, but there could be little objection to local therapy with any one of the latter agents. Prophylactic antibiotic therapy is more widely applied in other branches of medicine.[5o]

Reports have appeared in the literature concerning the use of penicillin as a prophylactic measure for the prevention of ophthalmia neonatorum.[24] Penicillin has been given intramuscularly or locally, in a combination of local and systemic administration, or intramuscularly combined with local use of silver nitrate. All forms of penicillin administration have compared favorably with the Credé prophylaxis in most observers' hands. Sorsby [6k] found that penicillin was the best agent in the treatment of actual clinical cases of ophthalmia neonatorum. Excellent results were obtained with penicillin locally, when repeatedly applied at very frequent intervals, and with intramuscular use of penicillin.

Trachoma.—There are numerous reports in the literature concerning the treatment of trachoma by local use of sulfonamides, systemic administration of sulfonamides, combinations of local and systemic administration of sulfonamides, and local use of chloramphenicol and aureomycin, with excellent results.[25] Although the trachomatous process seems to be quieted, the active ingrowth of the pannus formation was inhibited in only a few instances. There is still no definite evidence

24. Bickel.[3z] Finland.[5o] Halbrun, LePage, and Mawas.[6e] Rejchrt.[6f] Watts and Gleich.[6g] Davidson, Hill, and Eastman.[6h] Berwind.[6i] Candano, Cisneros, and Arelano.[6j]

25. Ainsle.[1b] Pijoan, Loe, and Payne.[6l] Tsopellas.[6m] Siniscal.[6n] Jebegian.[6o] Nataf.[6p] Ohturi.[6q] Magnol.[6r] Kamel.[6s] Boase.[6t] King and Robia.[6u] Smadel.[6v] Arakawa and Kitamura.[6w] Freyche.[6x]

that any of these agents attacks the etiologic factor of trachoma, and most of the observations suggest that they control secondary infection.

Ocular Viral and Rickettsial Diseases Treated with Antibiotics.—Unfavorable [26] and excellent [7b-g] results have been reported for the use of aureomycin locally in the treatment of dendritic keratitis. Experimental data have also varied, showing that in some hands aureomycin has been successful in controlling experimental herpes simplex of the rabbit cornea whereas in others the drug has failed.[27] Terramycin, chloramphenicol, and antihistaminics seem to have a retarding effect on the herpes-simplex keratitis of the rabbit eye.[41] Chloramphenicol and terramycin have shown possible benefit in clinical dendritic keratitis [41]; both aureomycin [7h] and chloramphenicol [4w] have been shown to have value in cases of herpes zoster ophthalmicus. Herpes keratitis was also found to be controlled by dihydroergotamine (DHE45), an ergot alkaloid preparation, when used locally in drops containing 1.0 mg. dissolved in 5.0 cc. of sodium chloride solution, instilled every one to two hours, and when therapy was combined with oral administration of ergotamine tartrate, 3 to 6 mg. daily.[7i] Methenamine may have some benefit in treatment of herpes corneae.[7j]

Aureomycin has been reported to be successful in treatment of molluscum contagiosum,[7k] disciform keratitis,[7b] scrub typhus,[7l] psittacosis, and lymphogranuloma.[7m] There are also reports of chloramphenicol and aureomycin being successful in cases of eczema vaccinatum, both generalized and localized to the lids.[7n-p] Aureomycin was not successful in treatment of conjunctivitis due to Newcastle's virus.[7q]

Miscellaneous Conditions.—There is some evidence that ethyl vanillate may be of value in treatment of histoplasmosis,[7r] and that aureomycin [7t] and "D. D. S." (4-4-diaminodiphenylsulfone) [5m] may be helpful in leprosy.

Selection of an Antibiotic.—By virtue of the information already available, it is apparent that most ocular infections due to bacteria should respond to antibiotics now obtainable. Some ocular infections due to viruses and rickettsias should also respond favorably.[1-10] Whenever possible, the ophthalmologist should be guided in his choice of antibiotic by cultures, smears, and sensitivity studies. Sometimes sensitivity studies may give erroneous results, and the final test and decision on the choice of an antibiotic rest with clinical trial. When one has a multiple choice of antibiotics, one should use the cheapest, the least toxic, and the easiest to administer. Preference should be given to the neomycin-polymyxin-bacitracin group, and perhaps, if Theodore's studies are confirmed, to sodium propionate. Preference is given to this group because it is effective against a wide variety of bacteria; and if sensitivity develops, these agents are less likely to be required for systemic administration later in the patient's life. Thus, if sensitivity occurs, the patient has lost very little. If an ocular infection does not seem to be responding to the chosen antibiotic after from 48 to 72 hr. of therapy, change to another antibiotic should be made. If the intraocular infection is severe and therapy does not seem to be halting the progress of the disease, a change can be made earlier.

One should beware of using combinations of antibiotics for which there is not definite information that they are additive, synergistic, and do not interfere with each other's action. One should consider the stability of solutions when solutions

26. Ainsle.[1b] Azzolini and Faldi.[6y] Pritikin, Duchon, and Farmer.[6z] McWilliam and Wilson.[7a]

27. Cannon, Leopold, and Shope.[41] Braley.[7h]

are prescribed; chloramphenicol is stable at room temperature, whereas aureomycin and terramycin, penicillin, and streptomycin preparations have to be refrigerated in order that their potency may be maintained. Aureomycin and terramycin, like other antibiotics, are much more stable in ointment preparations than in solution. When they are preferred in therapy of an ocular condition, the ointment may be used; however, it must be kept in mind that the ointment bases may interfere with epithelial regeneration. Some of these orally administered agents are more likely than others to produce nausea and vomiting, and, from experience, chloramphenicol seems to offend less than does aureomycin or terramycin in this regard. Chloramphenicol gives higher intraocular concentrations than either terramycin or aureomycin. This may be an important factor in the treatment of intraocular infections.

TUBERCULOSIS

Even with the progress made in the past few years, the ideal of the completely bacteriostatic drug which is capable of fending off the progress of tuberculous disease indefinitely has by no means been attained.[28] Paraaminosalicylic acid, which has a definitely antibacterial effect, is distinctly inferior to streptomycin.[29] However, when combined with streptomycin, it seems to have additive effects. Thiazolsulfone (promizole®) and glucosulfone sodium (promin®) preceded streptomycin and *p*-aminosalicylic acid, but neither has shown itself comparable to streptomycin and *p*-aminosalicylic acid. Neomycin,[30] has proved to be toxic in vivo, and efforts to produce a toxic-free product have not succeeded so far. Terramycin [31] has low toxic potentialities and may develop into a useful remedy for mild, long-term antibiotic effect.[32] Viomycin [33] is remarkably effective against the tubercle bacillus in vitro and in vivo but does not equal streptomycin weight for weight and has some toxic effects in its present, unpurified state. At the present time, the greatest antimicrobial therapeutic results, with the fewest undesirable effects, would be obtained with moderate doses of streptomycin sulfate combined with maximally tolerated doses of *p*-aminosalicylic acid.

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28. Long[1p] Missirolli.[1w] Bietti.[1x] Donegan.[1s] Peiqer.[2b] Hinshaw.[2g] Jones, Stearns, and Himmelstein.[2h] Woods, Wood, and Naquin.[2l] Missirolli.[2q] Pritikin, Duchon, and Farmer.[2s] Temple, and others.[2o] Spain and Childress.[2f] Hoggarth and Martin.[3j] Croshaw and Dickenson.[3k] Francis, Spinks, and Stewart.[3l] Steenken and Wolnsky.[4g] Bonavolanta and de Berardinas.[4l] Pejanney, Cox, and Grindall-Balchum.[4q] Whitmer.[5j] Aznar.[7t] Brognoli.[7u] de Ferrari.[7v]

29. Missirolli.[1w] Donegan.[1s] Rees and Robson.[2e] Weitzman, Cayley and Wingfield.[2l] Alvarez-Alvarez.[2k] Woods, Wood, and Naquin.[2l] Sykowski.[2n] Applemans, Michiels, Delfos, and van Assche.[2o] Missirolli.[2q] Das Gupta.[2r] Parisi.[2t] McLean.[2y] James, and others.[3d] Temple, and others.[3o] Spain and Childress.[3f] Hamburger, and others.[3g] Adcock, and others.[3h] Francis, Spinks, and Stewart.[3l] Bonavonlanta and de Berardinas.[4l] Salgado-Benavidas.[4p] Waldo and Tyson.[6d]

30. Duncan, Clancy, and others.[3n] Wolgamott and Duncan.[3o] Waisbren and Spink.[3p] Waldo and Tyson.[6d]

31. Caldwell, Spies, and Wolfe.[7w] Steinken and Wolussky.[7x] Hobby and others.[7y] Patelski.[8a] Hobby.[8b]

32. Wallner, Turner, and others.[2d] Steinken and Wolussky.[7x]

33. Werner, Tompsett, and McDermott.[1c] P'an, Halley, and others.[2q] Karlson and Gainer.[3r] Steenken and Wolensky.[3s] Youmans and Youmans.[3t] Hobb, and others.[3u] Ehrlich and others.[3v] Bartz, and others.[3w] Finlay, and others.[3x] Patelski.[8a] Hobby.[8b]

RUTIN

In 1936, Szent-Györgyi obtained evidence of a factor in citrus fruits and Hungarian red peppers, distinct from ascorbic acid. He designated it vitamin P because of its action in remedying increased capillary permeability and fragility. To this day, the chemical nature of vitamin P remains unknown. The use of rutin to restore to normal, increased capillary fragility and permeability in man was established in 1943 by Griffith, Lindauer, and Couch.[34] This was followed by numerous papers in medical, pharmacological, and chemical journals concerning the properties of rutin, and its use in hemorrhagic and other conditions.

Rutin may be described as a vitamin-P-active substance, which is easily accessible; stable against air and heat, and weak acids and alkalis, it is nontoxic in exact doses, and is highly active when given by mouth. It is a definite, uniform chemical compound of known structure, which can be administered in precise doses. It actually has been known for more than a century, having been discovered in 1842 by August Weiss, a Nuremburg apothecary, who obtained it from garden rue. From the vast study which is available, there is convincing proof that rutin is innocuous.[34]

There is evidence to suggest that rutin has an ascorbic acid-sparing effect and that rutin would hasten recovery after excessive irradiation. It has also been suggested that the property of controlling capillary permeability might be attributed to an effect on the tonus of the precapillary vessels. It has been suggested that preservation of sympathin by vitamin P or by rutin is responsible for this effect. This observation was first recorded in 1941 by Lavollay and Neumann. The problem was reevaluated recently.[35] The terminal vascular bed of the rat mesoappendix was used to determine the effect of rutin and other flavinoids on the response of smooth-muscle components to topically applied epinephrine. Intravenously injected rutin, 2.5 to 5.0 mg. per kilogram of body weight, reduced the epinephrine threshold to about 40% of the initial level. A dose of 1 mg. per kilogram was less effective. Other flavinoids also reduced the threshold of smooth-muscle components of the vascular bed to topically applied epinephrine.[35]

Although it has been suggested that rutin might block histamine and anaphylactic shock, there is little evidence to confirm this initial impression. Little evidence exists that rutin may inhibit the action of hyaluronidase. Quercetin and esculetin were able to inhibit histidine decarboxylates, but rutin was not. Beiler and coworkers [36] demonstrated that rutin and other flavinoids were able to inhibit choline acetylase.

Some evidence has also been presented that rutin might inhibit the Shwartzman reaction.[34]

Although there is considerable evidence that rutin reduces increased capillary fragility, there is still some question of its value in diabetic retinopathy. Results to date are not conclusive. Recent observations by Levitan [37] were unable to demon-

34. Couch, A. F.; Krewson, C. F., and Nagsky, J.: Chemistry, Pharmacology and Clinical Application of Rutin, AIC-291, United States Department of Agriculture, 1951.

35. Chrisnon, J. N.; Berez, R. R.; Madden, J. D., and Fuhrman, F. A.: Rutin and Other Flavenoids as Potentiators of Terminal Vascular Responses to Epinephrine and as Antagonists of Vasodepressor Materials, Am. J. Physiol. **164**:391, 1951.

36. Beiler, J. M., and others: Effect of Vitamin P Compounds on Choline Acetylase, Arch. Biochem. **26**:72, 1950.

strate any agent of this group that improved capillary fragility. Levitan [37] tested rutin, esculin, adrenoxyl, and vitamin E on the capillary fragility of patients with diabetic retinopathy. Barnes [38] also found that rutin was ineffective in prophylaxis and treatment of diabetic retinopathy. Hollenhorst and Wagener,[39] in 1949, from a review of the literature concerning rutin, concluded that further study was in order and that possibly something could be learned through the use of this drug of the degenerative complications in subjects with diabetes of long duration. Perhaps rutin may be of value if given before damage to the capillaries has developed. Glass [40] demonstrated that rutin was ineffective in lesions due to capillary bleeding when tests showed normal fragility. Bailliart [41] and Radnot and Sipos [42] reported some favorable effect with rutin on capillary fragility.

Obviously, the reported results of rutin therapy on diabetic retinopathy are variable.[43] Many factors contribute to the discrepancies: the condition of the vessels at the onset of therapy, the method of testing capillary fragility, dosage of rutin or other flavinoids, and the tendency to spontaneous temporary recovery. However, the bulk of the evidence is not favorable for improvement in existent diabetic retinopathy. The role of rutin in prevention in cases without preexisting vascular lesions has not been adequately evaluated to date.

STREPTOKINASE AND STREPTODORNASE

Evidence accumulated during the past 20 yr. has demonstrated that the catalytic agent streptokinase and the enzyme desoxyribose nuclease, or streptodornase, both derived from hemolytic streptococci, may be successfully employed as a highly useful topical adjunct to surgical or other treatment of certain acute and chronic infections, and in other disease situations in which clotting of blood or its elements creates a therapeutic problem.[44] These enzymes are produced in abundance during the growth of certain strains of hemolytic streptococci group A. Streptokinase apparently acts on a fibrolysing system present in the euglobulin fraction of human blood. The fibrin-lysing system is activated by this agent, which causes liquefaction of the fibrin. Streptokinase also inhibits the change of fibrinogen to fibrin. Streptokinase is antigenic, and an antikinase may develop in human beings as a result of antecedent hemolytic-Streptococcus infection. Streptodornase (desoxyribonuclease) is an enzyme having the capacity of hydrolyzing desoxyribonucleic acid.[45]

Streptodornase is well preserved if stored at approximately 4 C. Room temperature or heat greater than 4 C. will rapidly destroy this agent.

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37. Levitan, B.: Clinical Observations on the Effects of Injectible Rutin, Esculin, Adrenoxyl and Vitamin E on the Capillary Fragility of Diabetic Retinopathy, Am. J. M. Sc. **221**:185, 1951.

38. Barnes, R. H.: Capillary Fragility Studies in Diabetic Mellitus and Use of Rutin in Diabetic Retinitis, Am. J. M. Sc. **219**:368, 1950.

39. Hollenhorst, R. W., and Wagener, H. P.: Rutin, Am. J. M. Sc. **217**:223, 1949.

40. Glass, W. H.: Rutin Therapy in Diffuse Capillary Bleeding, ibid. **220**:409, 1950.

41. Bailliart, P.: Capillary Permeability, Ann. ocul. **183**:361, 1950.

42. Radnot, M., and Sipos, I.: Contribution to the Treatment of Diabetic Retinitis, Ophthalmologica **119**:373, 1950.

43. Bailliart.[41] Radnot and Sipo.[42] Dienstbier, E.: Rutin Therapy in Ophthalmology, Československ. ofth. **6**:75, 1950.

44. Miller, J. A.; Ginsburg, N.; Lipin, R. J., and Long, P. H.: Clinical Experiences with Streptokinase and Streptodornase, J. A. M. A. **145**:620 (March 3) 1951.

45. Kunitz, N.: Crystalline Desoxyribonuclease, J. Physiol. **33**:349, 1950; Crystalline Desoxyribonuclease: Kinetics of Reaction, ibid. **33**:363, 1950.

Lederle Laboratories Division of the American Cyanamid Company produces a mixture of these compounds. This mixture has a potency of roughly 200,000 units of streptokinase and 300,000 units of streptodornase per ampule. The material is prepared for use by dissolving the contents of one ampule in 20 cc. of sterile isotonic sodium chloride solution. It is readily soluble, and should not be shaken. It should be used immediately after preparation, as it loses its potency rapidly at room temperature. There is no indication of any antagonism between the action of streptokinase or streptodornase and that of sulfonamides or antibiotics.

Euglobulin must be present, as well as magnesium and manganese, for these agents to work. According to Miller and his co-workers,[44] these agents appear to be therapeutically active in serous, purulent, or hemorrhagic exudates if contact can be maintained for four to six hours. This is true also of the catalytic action of streptokinase, leading to the lysis of clotting blood. Foreign bodies and slough interfere with the action of these substances. Leucocytes, scar tissue, and healthy tissue are not affected by streptokinase or streptodornase. No allergic reactions have been reported to these substances. A dose of 400 to 500 units of streptokinase is necessary to prevent the coagulation of 1 cc. of blood. No report on the use of these agents in ophthalmology—in intraocular hemorrhage or infections—has appeared to date, although it has been used in cases of tuberculous meningitis.[46]

It may be of practical importance to note the reported control of pulmonary hemorrhages brought about by the use of intravenous injection of posterior pituitary U. S. P.[47]

Snake venom also has a fibrolytic effect.[48]

TANTALUM AND WOUNDS

Although tantalum is malleable, and not toxic, complications may arise from its use. Eleven cases are reported by Mirowsky and his co-workers.[49] Removal of the tantalum plate was necessitated by formation of a large, infected epidural granuloma, symptoms of which appeared in from one week to three months after insertion of the plate. An infected granuloma was found in 10 of these 11 cases. Although the metal may be noncytotoxic, it is still a foreign body that is often poorly tolerated by tissues harboring infectious organisms. It is likely that the granuloma represents not a specific reaction to tantalum but a general foreign-body reaction by infected tissue. It is possible that this reaction can be prevented by not inserting tantalum in any infected area. Tantalum drains have been employed in treatment of glaucoma.[50]

MYASTHENIA GRAVIS

The use of alkyl phosphate anticholinesterase agents in the treatment of myasthenia gravis has caused considerable interest in the last few years. Diisopropyl

46. Williams, S., and Bazeley, P. L.: Use of Streptokinase in Treatment of Tuberculous Meningitis, M. J. Australia **2**:690, 1950.

47. Trimble, H. G., and Wood, J. R.: Pulmonary Hemorrhage as Controlled by the Use of Intravenous Pituitrin, Dis. Chest **18**:345, 1950.

48. Janszky, B.: Solubility of Fibrin Clots Produced by Thrombin and by Snake Venom, Science **112**:173, 1950.

49. Mirowsky, A. N.; Hazouri, L. P., and Greiner, E. J.: Epidural Granuloma in the Presence of a Tantalum Plate, J. Neurosurg. **7**:45, 1950.

50. Wynne Parry, P. G.: Use of Tantalum Drains in Glaucoma, Brit. J. Ophth. **34**:684, 1950.

fluorophosphate, hexaethyltetraphosphate, and tetraethylpyrophosphate have all been used. While tetraethylpyrophosphate proved to be the most effective of these,[51] it had two disadvantages—toxic manifestations were frequent, and it was rapidly hydrolyzed when exposed to moisture. These actions seemed to be characteristic of cholinergic phosphate, in which all the alkyl groups in the molecule are linked to phosphorus by means of oxygen atoms. Octamethyl pyrophosphoramide, which lacks the alkyl oxyphosphate linkage, is a colorless liquid with a faint taste similar to that of black pepper. It is soluble in water and most organic solvents. According to Rider and others,[52] this compound was first synthesized by Shrader and found to be a systemic insecticide by Kükenthal.

DuBois, Doull, and Coon [52b] have studied the pharmacology and toxicology of octamethyl pyrophosphoramide. This compound is a potent anticholinesterase agent, with a selective action on peripheral cholinesterase. Octamethyl pyrophosphoramide is apparently stable and is only slowly hydrolyzed in dilute aqueous solution. In would require more than six months for only a 10% decomposition to occur at 20 C. Hydrolysis is accelerated greatly by acid, but only slightly by alkali. This is in great contrast to diisopropylfluorophosphate, which is quite unstable in aqueous solution. This agent can replace neostigmine in treatment in some cases of myasthenia gravis and has the advantage that two oral doses of from 9.5 to 18.0 mg. a day result in eventually maintained strength, which is generally greater than the maximal strength with neostigmine.

There is mutual potentiation of toxic side effects when neostigmine and octamethyl pyrophosphoramide are taken together. Since this is most pronounced in patients with severe myasthenia gravis, transfer from neostigmine to the new compound with such patients may be difficult, or even impossible.

It is known that compounds, such as curarine and curarine-like agents, will make patients with myasthenia gravis worse. Tests have been devised utilizing this information.[53]

HYALURONIDASE

Hyaluronidase is being employed in ophthalmologic practice. Its uses have been reviewed by Lebensohn.[54] He points out, as has been shown by others, that the combination of hyaluronidase with procaine increases diffusion of the anesthetic and speeds up the onset of anesthesia. The enzyme can be employed for retrobulbar injections by the Van Lint and O'Brien techniques. It does not seem to facilitate the passage of substances through the cornea. However, it may be helpful in the intraocular penetration of subconjunctival injections of antibiotics. Lebensohn also believes that the subconjunctival injections of hyaluronidase may improve corneal nutrition by increasing the permeability through the limbus.

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51. Atkinson, W. J., Jr.: Treatment of Myasthenia Gravis with Tetraethyl Pyrophosphate, South. M. J. **43**:865, 1950.

52. (*a*) Rider, J. A., and others: Treatment of Myasthenia Gravis with Octamethyl Pyrophosphoramide, J. A. M. A. **145**:967 (March 31) 1951. (*b*) DuBois, K. P.; Doull, J., and Coon, J. N.: Studies on the Toxicity and Pharmacological Action of Octamethyl Pyrophosphoramide, J. Pharmacol. & Exper. Therap. **99**:376, 1950.

53. Dunde, J. W.: Gallamine in the Diagnosis of Myasthenia Gravis, Brit. J. Anaesth. **23**:39, 1951.

54. Lebensohn, J. E.: Hyaluronidase in Ocular Surgery and Therapy, Am. J. Ophth. **33**:865, 1950.

Kadin [55] found that the use of hyaluronidase in a case of thyrotropic exophthalmos actually increased the edema and measurable proptosis. Others [56] have also noted the beneficial effects of hyaluronidase in methods of local anesthesia. Woodin [56b] was unable to demonstrate a spreading action of hyaluronidase on the normal cornea. This was tested on both the rabbit and the ox cornea.

Von Sallmann [57] found that strong solutions of hyaluronidase would produce irritation of the anterior and posterior segments, whereas weak solutions caused disappearance of red cells from the vitreous only slightly. Strong solutions were much more successful in this regard.

Heterologous hyaluronidase is much more irritating than the homologous enzyme. Homologous hyaluronidase also causes disappearance of red blood cells, and the inflammatory changes are much less severe.

LYSOZYME

Using the viscosimetric method for measuring lysozyme, Regen [58] found the lysozyme content of normal tears generally between 1,000 and 2,000 units per cubic centimeter. There was no demonstrable variation with age or sex, but there did seem to be a daily variation in the concentration. The lysozyme content of the tears was low in pathologic conditions associated with excessive tearing, as had been reported previously. Regen also found the lysozyme content decreased in keratoconjunctivitis sicca and in corneal dystrophy.

Hobart [59] treated a number of external ocular condition studies with lysozyme. His results were favorable.

ANTIHISTAMINICS

An antihistaminic substance has been defined as one that is capable of diminishing or preventing several of the pharmacologic effects of histamine, by mechanisms other than the production of pharmacologic responses diametrically opposed to those produced by histamine. Epinephrine is, therefore, not an antihistaminic, although it produces hypertension and other pharmacologic actions opposed to those of histamine.

It has been suggested that the antihistaminic substance attaches to the effector cell in a manner which prevents the action of histamine on the cell.[60] Burn [61] points out that antihistaminic compounds also possess atropine-like and dibenamine®-like actions. They exert a depressing action on muscle, resembling that of quinidine and quinine. They also are local anesthetics, and they inhibit the spreading action of hyaluronidase. It is important in clinical therapeutics, as well as in pharmacology, to emphasize that these drugs are not simply antihistaminics. They actually depress

55. Kadin, M.: Hyaluronidase in Thyrotrophic Exophthalmos, Am. J. Ophth. **33**:962, 1950.

56. (*a*) Venco, L.: Hyaluronidase in Ocular Anesthesia, Rass. ital. ottal. **19**:317, 1950. (*b*) Woodin, A.: Hyaluronidase as a Spreading Factor in the Cornea, Brit. M. J. **34**:375, 1950.

57. von Sallmann, L.: Experimental Study on the Vitreous: Experiments on Disappearance of Red Blood Cells from the Vitreous, Arch. Ophth. **43**:638 (April) 1950.

58. Regen, E.: Lysozyme Content of Tears, Am. J. Ophth. **33**:600, 1950.

59. Hobart, C.: Lysozyme in the Treatment of Ophthalmic Conditions, Am. J. Ophth. **33**:9, 1950.

60. Farrar, G. E., Jr.: A Review of the Therapeutic Application of Antihistaminics, Pennsylvania M. J. **54**:31, 1951.

61. Burn, J. H.: Pharmacologic Action in Antihistamine Compounds, Brit. J. Med. **2**:691, 1950.

the reaction of many tissues to many stimuli. Thus, the rather varied therapeutic applications of many antihistaminic drugs become less mysterious. According to Farrar,[60] most of these compounds possess the general formula (R–X–C–C–N —), in which R indicates a variety of benzene or heterocyclic structures containing carbon and hydrogen, and often nitrogen, sulfur, and oxygen. X may be nitrogen, oxygen, or carbon; when X is nitrogen, a familiar example is tripelennamine hydrochloride (pyribenzamine® hydrochloride). Most of the commercially available antihistaminics belong to this chemical group. When X is oxygen, a familiar example is diphenhydramine hydrochloride U. S. P. (benadryl® hydrochloride). When X is carbon, a familiar drug is prophenpyridamine N. N. R. ("trimeton"). A fourth group of these drugs is exemplified by antazoline hydrochloride N. N. R. (antistin®). This chemical classification, according to Farrar,[60] is useful in therapeutics, for some patients respond to members of one of these groups better than to others. If a given drug fails, or causes untoward side effects, substitution of a compound belonging to another chemical group is indicated. The physician should be familiar with about five of these agents. These antihistaminic compounds can overcome increased capillary permeability, cutaneous wheal and flare, release of epinephrine from the adrenal gland, and other pharmacologic actions of histamine.

Other actions of antihistaminic compounds are also variable. They may (1) be atropine-like (antiacetylcholine); (2) exert a local anesthetic effect, like procaine, but more irritating; (3) act as a hypnotic, like scopolamine; (4) have a weak quinidine-like action; (5) potentiate or inhibit epinephrine action. In general, the compounds in which X is nitrogen are the most active antihistaminics; those in which X is oxygen cause more hypnotic action.

The antihistaminics do not interfere with the formation of antibody in response to antigen, although they minimize the untoward effects of the union of antigen and antibody in the tissues. In the skin-testing with allergens, the antihistaminics inhibit the erythema, but do not eliminate the wheal or shorten the period produced by the substance to which the patient is sensitive. Untoward effects include sedation, dizziness, dryness of the mouth, weakness, nausea and anorexia, nervousness, headache, polyuria, heartburn, reduction in potency, diplopia, sweating, dysuria, and, rarely, dermatitis. Intolerance to one drug does not mean untoward reactions toward all the antihistaminic drugs. Drowsiness is often a desirable therapeutic effect, particularly at bedtime or in instances in which anxiety secondary to allergic disorder or other causes aggravates the disease under treatment. However, in a working patient drowsiness is undesirable.[60]

Cases of death from the administration of antihistaminic drugs are reported.[62] The majority of these occurred in children, who seem to be particularly predisposed to convulsions from overdoses. Agranulocytosis is another serious development. The toxic effects of antihistaminic agents have been classified [62] as those affecting the nervous system and special sense organs, and those affecting the gastrointestinal, cardiovascular, respiratory, genitourinary, cutaneous and mucosal, and hematologic systems. A number of these antihistaminics have an atropine-like action, which would cause dilation of the pupil. This should be kept in mind in dealing with patients with glaucoma, particularly of the narrow-angle type.

62. Wyngaarden, J. B., and Seevers, N. H.: Toxic Effects of Antihistaminic Drugs, J. A. M. A. **145**:277 (Feb. 3) 1951.

Vestibular toxic effects of streptomycin can be partially controlled by the use of dimenhydrinate ("dramamine").[10q]

Several new antihistaminics have been formed.[63] One of these is an antihistaminic of vegetable origin extracted from the gallnut. It appears to act for 20 to 18 hr., as compared with the maximal effect of 10 hr. with previously employed antihistaminics.[64]

There is definite evidence that antihistaminics may alter streptomycin blood concentrations,[10j] and that antihistaminics have a central-nervous action.[65] Another side effect of so-called antihistaminics is their ability to produce a conduction block of nerve fibers.[66]

The toxicity of histamine in mice is increased 50 to 100 times by adrenalectomy.[67] Histamine blocked the wheal following iontophoresis with methacholine (mecholyl®).[68] Histamine caused hyperactivity of the adrenal cortex. Antihistaminics failed to block this effect.[69] Perhaps histamine produces this effect by liberating epinephrine from the adrenal medulla, and this, in turn, stimulates the adrenal cortex.

Tepperman and co-workers [70] found a slight blocking effect of tripelennamine hydrochloride and phenoxadrine on the action of histamine phosphate injection U.S.P. on the ascorbic-acid content of the adrenal. Diphenhydramine (benadryl®) hydrochloride had no effect, but antihistaminics had no influence on the stress effect following the injection of carbon tetrachloride.

D-catechin is an anti-histidine-decarboxylase. Histidine decarboxylase has been demonstrated to aid in the production of histamine in vivo. Chemicals effective in controlling the activity of histidine decarboxylase should be active in preventing the formation of histamine. Because of the well-known limitations of the antihistaminic agents, the concept of the anti-histidine-decarboxylase is interesting. Chunn [71] found some benefit from use of *d*-catechin in urticaria, but none in eczema

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or atopic dermatitis. Obviously, the aim of anti-histidine-decarboxylase therapy is to prevent histamine formation. Schultz[72] also reports some favorable results with the combination of an anti-histidine-decarboxylase and antihistaminics in the therapy of various allergic states. Favorable results with antihistaminics are reported in ophthalmic diseases.[73]

As a guide in therapy, Kahan[74] recommends measuring the polymorphonuclear cell count and the blood complement. If the polymorphonuclear cell count is decreased or is initially low and the complement content of the blood increases during the first few days of treatment with antihistaminics, the prognosis is favorable. If one finds a high eosinophil and a high epithelial cell count in conjunctival smears, the chances are that the results will be favorable.

By colorimetric tests, d'Ermo[75] was able to show that subconjunctival and conjunctival applications yielded higher intraocular concentrations than either the intravenous or the subcutaneous route of administration. Dimethylaminoethylbenzylaniline (antergan®) and pyrilamine maleate (neo-antergan® maleate) reduced the permeability of the blood-aqueous barrier; antazoline did not. Diphenhydramine and tripelennamine hydrochloride produced a mild reduction in blood-aqueous permeability.

Antihistaminics have some value in the management of motion sickness.[76]

CORTISONE AND CORTICOTROPHIN (ACTH)

The medical world has been deeply interested in, and actively concerned with, hormonal therapy since the advent of corticotrophin (ACTH) and cortisone into the therapeutic "pharmamentarium." Ophthalmologists have been no exception. Experimental work is proceeding rapidly, as well as clinical trials with these agents in almost all varieties of disease. Since the review of pharmacology in 1950, it has become evident that the initial observations of the dramatic effect of cortisone and corticotrophin in ocular diseases have been well substantiated.[77-79]

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(*Footnote continued on next page*)

It is also evident that the action of corticotrophin and cortisone is a pharmacologic, and not a physiologic, one, and that it is not specific for any one disease, but works through a general palliative, protective, and suppressive mechanism. Corticotrophin and cortisone do not cure any ocular disease (Table 8). Nevertheless, they appear to be exceedingly valuable, and even vision-saving, through their ability to protect the ocular structures by blocking the ravages of disease.

There has been practically no attempt reported in the literature at the use of adrenal-cortex steroids other than cortisone in the therapy of ocular diseases, but it is evident from the experiences in other fields that no steroid, with the possible exception of compound F, approaches cortisone in therapeutic effect.[77a] In general, the ocular effects of cortisone and those of corticotrophin are about the same.[77b-g] Cortisone has the advantage of being active locally.[80] The aim of any hormone

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80. Scheie, and others.[77d] Woods.[77g] Footnotes 77.[b-o]

therapy is to secure the maximum effect with the smallest possible amount of the hormone. Dosage schedules based on the experiences of many ophthalmologists are included in Table 12.[77b-r] It must be realized that several of the unfavorable results may be due to inadequate dosage, particularly as applying to local therapy. It may be that failures in treatment of inflammatory processes of the posterior segment are due to inadequate dosage when the drug is tried locally. The agent may not be reaching the posterior segment in sufficient concentration.

Results of Therapy

The results of therapy are recorded in Tables 9, 10, and 11.

These data are derived from the articles available in the literature,[77b-r] and are not final. It is obvious that in any study of a clinical nature controls are difficult.

Table 8.—*Ocular Diseases Treated with Corticotrophin (ACTH) and Cortisone*

Ocular Disease	Possible Mechanism of Action
Collagen diseases	Inhibit permeability
e. g., Ocular lesions associated with Rheumatoid arthritis Rheumatic fever Lupus erythematosus Dermatomyositis Scleroderma	Inhibit hyaluronidase Inhibit fibroblast activity
Allergies	
e. g., Contact dermatitis { drugs, bacteria	Inhibit permeability
Blepharoconjunctivitis	Inhibit inflammatory reaction
Phlyctenular keratoconjunctivitis Periarteritis nodosa Uveitis Sympathetic ophthalmia Phacoanaphylaxis	Alter histamine metabolism
Inflammatory disease	
e. g., Keratitis { Bacterial Viral	Not by direct effect against organism but perhaps by: inhibition of permeability inhibition of inflammatory reaction
Tumors	Lymphocytolytic
e. g., Lymphomas Hodgkin's disease Leukemia	
Myasthenia gravis	Lymphocytolytic (?) (thymus) Cholinesterase (?)
Burns	Antishock (electrolyte metabolism) Inhibit permeability Inhibit fibroblast activity Blocking of antibodies (?) or antigen-antibody effects (?)

One cannot always be certain whether the ocular disorder would have benefited by other forms of therapy, or with no particular therapy, whether the improvement was due to natural resistance or to the addition of the cortisone or corticotrophin, or whether the failures were due to inadequate dosage schedules. Nevertheless, this uncertainty does not prevent one from making tentative conclusions, as long as it is understood that these are subject to future change as the increasing data demand.

Administration of the Hormones.—There are many advantages to the local use of cortisone[81]: (1) There is little danger of systemic reaction; (2) the cost to the patient is less; (3) hospitalization is not necessary, and (4) local treatment can continue probably almost indefinitely, no deleterious effects having been reported

81. Scheie, and others.[77d] Woods.[77g] Footnote.[77k-o]

TABLE 9.—*Corticotrophin (ACTH) and Cortisone Therapy; Encouraging Results* *

	Local	Systemic
1. Blepharitis—allergic (drugs, bacterial)	+	..
Blepharoconjunctivitis	+	..
Tumors—Hodgkin's disease, leukemia, lymphoma	..	+
Vernal conjunctivitis		
Early stages	+	..
Late stages	..	+
2. Episcleritis	+	..
3. Keratoconjunctivitis		
(*a*) Marginal ulcer	+	..
(*b*) Phlyctenular	+	..
(*c*) Acne rosacea	+	..
(*d*) Allergic type	+	..
(*e*) Superficial punctate type	+	..
4. Keratitis		
(*a*) Sclerosing keratitis	+	..
(*b*) Tuberculous	+	..
(*c*) Keratitis profunda—early	+	..
(*d*) Acute interstitial		
Specific	+	..
Nonspecific	+	..
5. Uveitis		
(*a*) Anterior		
Acute nongranulomatous	+ and/or	+
Postoperative	+ and/or	+
(*b*) Posterior		
Acute focal choroiditis	..	+
(*c*) Diffuse		
Phacoanaphylaxis and retained lens material	+ and	+
Acute nongranulomatous	+ and	+
Early sympathetic ophthalmia	+ and	+
(*d*) Hypertensive uveitis	+ and/or	+
6. Burns		
Chemical	+ or	+
Thermal	+ or	+

* Either complete remission or with relapse that responded to continued therapy—almost unanimous agreement among investigators to date.

TABLE 10.—*Corticotrophin and Cortisone Therapy: Questionable Results* *

	Local	Systemic
Keratitis		
Chemical	+	..
Recurrent erosion	+	..
Dendritic	+	..
Metaherpetica	+	..
Herpes zoster	+ and/or	+
Keratoplasty	+ and/or	+
Profunda—advanced	+	..
Syphilitic—advanced	+ and/or	+
Uveitis		
Anterior—advanced granulomatous	+ and	+
herpes zoster	+	..
Posterior—advanced granulomatous and nongranulomatous	..	+
e. g., Sympathetic ophthalmia	..	+
Sarcoid	..	+
Neuritis		
Optic and retrobulbar	..	+
Retrobulbar fibroplasia	..	+
Myasthenia gravis	..	+
Central angiospastic retinitis (edema and hyperemia)	..	+

* Pathologic conditions of the eye in which favorable results and also failures are reported but favorable results predominate slightly.

from continuous local therapy to date; (5) high concentrations are possible. Dosage schedules are listed in Table 12. These are working schedules which give results to date. There is no doubt they will have to be altered as more information is obtained.

Undesirable Side Effects of Corticotrophin and Cortisone When Systemically Administered.[77]—A number of unfavorable effects have followed systemic administration of these drugs:

1. Gastrointestinal hemorrhage, presumably in some cases due to activation of peptic ulcer.

2. Hemolytic crises and sickle-cell anemia.

3. Myocardial failure due to hydremia resulting from salt retention, occurring in cases with an already damaged heart.

TABLE 11.—*Corticotrophin and Cortisone Therapy: No Improvement* *

	Local	Systemic
Pemphigus	+	..
Erythema multiforme and Stevens-Johnson disease	+	..
Corneal dystrophy	+	..
Rodent ulcer of cornea	+	..
Mustard-gas keratitis	+	..
Uveitis		
Chronic diffuse granulomatous uveitis	+	..
Harada's disease	+	+
Vogt-Koyanagi disease	+	+
Chronic Still's disease	+	+
Eales's disease	+	+
Angiospastic retinopathy (pigmentary changes)	..	+
Thyrotropic exophthalmos	..	+
Junius Kuhn and macular degeneration	..	+
Senile macular degeneration	..	+
Pigmentary retinal degeneration—primary	..	+
Angioid streaks	..	+
Optic atrophy	..	+
Glaucoma—primary	..	+

* Ocular diseases in which majority of results have been poor.

TABLE 12.—*Recommended Dosage Schedules* *

Cortisone Acetate	
Cortisone-acetate suspension	
Ointment	Undiluted—1:4 in isotonic NaCl Sol. or benzalkonium chloride 1:5,000 25 mg./cc.—5 mg./cc. or 25 mg./gm.—12.5 mg./gm. in aquaphor*
Subjunctival	12.5 mg.—1.25 mg.
Systemic	
Intramuscular	
In adults	100 mg. every 8 hr. for 3 doses 100 mg. every 12 hr. for 2 doses 100 mg. daily, thereafter
Orally	Same schedule
Corticotrophin	
Systemic	
Intramuscular injection	infants 2 mg. every 6 hr. adults 20 mg. every 6 hr.

* Solutions are applied every hour to twice daily, depending on stage of disease and response. Ointments are usually used once to four times daily alone, or in combination with drop therapy, depending on course of disease. Duration of therapy is determined by response to therapy and to cessation of therapy.

4. Hypertension, resulting in cardiovascular accidents.

5. An increased tendency to venous clotting, thrombosis, and embolism. This was observed to persist as long as one to two weeks after cessation of ACTH and cortisone therapy. In a series of 175 cases, 7% of thromboembolic episodes occurred, with two deaths.

6. Psychoses, occasionally.

7. A possible unfavorable influence on infections. Accumulating evidence suggests that this may occur. Patients receiving cortisone appear to be more susceptible to head colds. It has been shown that mice and hamsters are more susceptible to poliomyelitis virus when treated by cortisone. Patients with malaria suffer a relapse when treated with these drugs. Pulmonary tuberculosis may be activated by use of these agents. Local infections at the site of cortisone injection appear to be commoner than infections accompanying other types of intramuscular injection.

8. Possible atrophy of the adrenal cortex after long-range therapy with cortisone and atrophy of the pituitary with corticotrophin. These changes may appear to be reversible on withdrawal of the respective drugs. There is some evidence of reduction in thyroid function. It is possible that this may lead to atherosclerosis on a long-range basis, as seen in Cushing's disease (pituitary basophilism).

9. Possible lack of response to cortisone and corticotrophin with prolonged use of these agents.

10. Less serious complications, such as acne, hirsutism, obesity, insomnia, euphoria, increase in severity of diabetes, transitory deafness, renal glycosuria, and bradycardia.

11. Retardation of healing. This effect is not limited only to systemic administration but may also occur with local use.

Many of these complications do not concern the ophthalmologist, who will rarely employ drugs for such long-continued therapy. However, if he does, he should avoid the use of these agents in cases of peptic ulcer, pulmonary tuberculosis, myocardial disease, hypertension, old age, psychotic personality, malaria, or sickle-cell anemia, and in cases of recent operation, in which interference with wound healing would be serious. To prevent hydremia, limitation of sodium intake, by administration of ammonium chloride as a diuretic, and the use of mercurial diuretics may be helpful. It has been suggested that the use of estrogen may be of value in controlling acne, and testosterone in preventing excessive nitrogen loss.[17a]

Actions of Cortisone.—There is no doubt that cortisone favorably influences a variety of ocular diseases. However, the mechanism through which cortisone brings about this improvement has not been established. Certain facts are known concerning cortisone activity. These are listed in Table 13, after Paschkis.[77t]

Carbohydrate and Protein Metabolism: It is fairly well established that cortisone will increase the breakdown of protein and will interfere with the utilization of sugar. In other words, it has an anti-insulin activity and tends to increase the severity of diabetes in affected patients.

Electrolyte Metabolism: In the initial stages of therapy, cortisone will lead to a loss of sodium chloride and potassium. With prolonged treatment and with large doses, sodium will be retained. Alkalosis will develop, with loss of potassium

and chloride. There may also be loss of calcium and phosphorus. It is important that physicians who are planning to use large doses of cortisone familiarize themselves with the appearance of potassium deficit and metabolic alkalosis. Patients undergoing such a change may show apathy, lethargy, nervousness and irritability, muscular weakness, abdominal distention, occasional confusion, disorientation, delirium, muscular twitching, and tetany. Electrocardiographic changes and occasional arrhythmia, edema, hypochloremia, hypoproteinemia, and hypophosphatemia may also result. A prompt reversal of the clinical and blood-chemical abnormalities occur in such patients with administration of adequate amounts of potassium. In order to prevent the development of these symptoms, potassium, and perhaps phosphate ions, should be supplied to the patient during the course of therapy. Eliel and his co-workers [77u] suggest that this picture may occur after surgical procedures, and that it is probably due to adrenal hyperfunction resulting from surgical trauma.

TABLE 13.—*Actions of Cortisone* *

1. Carbohydrate and protein metabolism...	Representative of "sugar hormone" Increased protein catabolism and gluconeogenesis Decreased carbohydrate utilization; anti-insulin effect; diabetogenic
2. Electrolyte metabolism.....	Relatively weak. Initially: Na, Cl, K loss After prolonged therapy with large doses: Na retention. Alkalosis: K and Cl loss Loss of Ca and P.
3. Blood cells.....	Lymphopenia (lymphocytolytic), eosinopenia (mechanism?); stimulation of red and white bone marrow
4. Tissue cells.....	Inhibition of fibroblastic activity; stimulation of macrophage activity
5. Membrane permeability.....	Decreased; therefore decrease of inflammatory or allergic transudation and cell extravasation
6. Renal	(*a*) Electrolyte reabsorption (see 2) (*b*) Decreased glucose reabsorption (= lowered renal threshold) (*c*) Increased uric-acid clearance
7. Histamine metabolism.....	(*a*) Increased excretion of histidine (*b*) Decreased formation of histamine (*c*) Increased breakdown of histamine by histaminase (see 8)
8. Enzymes	(*a*) Inhibits hyaluronidase (see 5) (*b*) Stimulates histaminase (see 7) (*c*) Various; arginase +, lysozym —
9. Immune reaction.....	Controversial. "Delayed" (= tuberculin type); reaction inhibition (?); little influence on antibody formation; "blocking" of antibody actions (?)

* After Paschkis.[77t]

CORTISONE AND INFECTIONS

There is evidence that cortisone, locally applied, will decrease the severity of experimental bacterial keratitis, produced by organisms such as Aerobacter aerogens, P. vulgaris, Escherichia coli, Pneumococcus Type 1, and Staphylococcus aureus.[77m] Local cortisone therapy did not lead to a cure of these lesions, but reduced some of the signs of inflammation. On the other hand, similar experiments with virus keratitis in rabbit eyes showed that cortisone administered locally had no significant influence on the experimental lesion when used in the form of drops. When used subconjunctivally, it actually increased the severity of the resultant lesions, as compared with the control eyes.[77m] Systemic administration of cortisone and corticotrophin, as demonstrated by Hallet, Leopold, and Steinmetz,[77v] actually reduced the severity of the lesion for the first five days, but after this there was no difference between the eyes of treated rabbits and the eyes of untreated rabbits.

Loosli and associates [77w] were unable to demonstrate any beneficial effect of corticotrophin on the course of experimental influenza-virus-Type-A infections. Kilbourne and Horsfall [77x] reported that the concentration of influenza or mumps viruses obtained in developing hen's eggs injected with cortisone exceeded that in similarly infected control eggs by a significant amount.

Schwartzman [77y] claims that intramuscular injections of cortisone in hamsters, which naturally have considerable immunity to poliomyelitis virus, transformed a negligible illness into a rapid, violent, and uniformly fatal disease. Corticotrophin alone, however, did not affect or influence the course of the poliomyelitis in the hamster, as compared with that in untreated controls.

Experiments have been carried out with tuberculosis in experimental animals to determine the effect of cortisone. Michael and his co-workers [82] noted that albino rabbits with some natural resistance respond to infection with the human tubercle bacillus with a chronic, granulomatous, nonfatal process, in which caseation is not conspicuous, whereas the animal treated with cortisone and similarly infected with tubercle bacilli dies of tuberculosis in the majority of cases. Striking histologic differences were noted. Localized granulomas were seen in the organs of the animals given injections only of tubercle bacilli, whereas the lesions in animals also receiving cortisone were diffuse and contained fewer inflammatory cells. The influence of cortisone, Michael and his co-workers concluded, on experimental tuberculosis appeared to be a lowering of the host's natural resistance. Lurie and co-workers,[78a] in an endeavor to identify the constitutional factors responsible for the genetic resistance of susceptibility to tuberculosis of highly inbred rabbit races, found that an administration of estrogen to susceptible rabbits materially increased their resistance, whereas the periodic exposure of resistant rabbits to chorionic gonadotropin N. N. P. enhanced the susceptibility to disease. It was noted in the report of Lurie [78c] that tuberculosis in rabbits was accompanied with marked hypertrophy of the adrenal cortex. In later studies, it was observed that the degree of hypertrophy of the adrenal cortex of natally resistant rabbits infected with tuberculosis is much greater than that of susceptible rabbits similarly infected. Therefore, investigations on the role of the adrenal cortex in the resistance to disease were begun. The general plan of this group was to determine whether, by increasing the adrenal function, resistance can be increased and, conversely, whether by lowering this function the rate of resistance can be diminished. It appeared from their studies with cortisone that this hormone increased the phagocytic activity of the reticuloendothelial cells and also the alveolar macrophages. Actually, the cortisone-treated rabbits generated more tubercles than did the controls, which did not receive cortisone. However, the size of the tubercle and their spread underwent uniform and striking reduction in the cortisone-treated animals. The spread of disease to lymph nodes and other organs was also greatly reduced in the experimentally treated animals. The cortisone, instead of increasing the destruction of bacilli, actually greatly increased their numbers in the lesions. Although the number of tubercle bacilli in the lungs of cortisone-treated rabbits was greater than in the lungs of the controls, the dissemination to draining tracheobronchial lymph nodes was very much less than in the control animals.

82. Michael, Cummings, and Bloom.[77z] Lurie and others.[78a] Spain and Molomut.[78b]

Hahn and his associates [78d] found that patients receiving cortisone in the presence of streptococcal infection exhibited fever for a longer period than did the controls. Neither did cortisone therapy appreciably alter the antistreptolysin response. During the first six days there was a slight decrease in the antistreptolysin titers, but within two to three weeks the antibody titer was higher than in the untreated patient. Since cortisone is not antibacterial, this may indicate that bacteria were still present, and were there to stimulate antibody formation.

Both Mogabgab and co-workers [78e] and Glaser and his co-workers [78f] found that in experimental infections of the eyes systemic use of cortisone gave rise to poorer results than in the control eyes. Cortisone apparently suppresses the response of the host to larger numbers of spirochetes, while at the same time spirochetes are multiplying without restraint. Until more is known about the effect of cortisone on the host-parasite relationship in syphilis, it would seem unwise to give the drug to patients with this disease. A rebound phenomenon in man could be particularly dangerous, as, for example, in syphilitic involvement of the optic nerve or of the coronary arteries.[78g]

It has been demonstrated that cortisone, although it has no effect on the typhoid organism itself, does reduce the apparent severity of a disease through its effect on the host.[41] This immediately raises the question as to whether or not antibiotics should be used with cortisone in the control of infectious diseases, or whether there is a likelihood of an infectious process developing while the patient is under cortisone therapy. This has been answered in part by experiments in which cortisone and chloramphenicol were combined for the treatment of typhoid. Here it was found that quicker relief occurred when these two agents were used in the therapy.[78i] Thus, it becomes apparent that with the combination of antibiotics and cortisone better results may be obtained in treatment of infection.[78b, i] There are instances of cortisone being effective in infections in human beings. This probably means that the cortisone exerts its effects, the host manifests a less serious disease, and the infection is overcome by the natural resistance of the patient.

It is evident from these reports that cortisone therapy in the presence of infection may be exceedingly dangerous.[78j] The etiologic organism is not killed by the cortisone. Its growth is apparently not inhibited. However, the signs of inflammation are reduced by virtue of the blocking action of the cortisone. Thus, one may be lulled into a sense of security and a feeling that the patient is improving, whereas the organisms are actually multiplying, and as soon as cortisone therapy is removed the organisms may blossom into a ravaging, and perhaps uncontrollable, infection. There is also the possibility that if one uses large doses of cortisone over a sufficient period of time in conditions which are primarily not bacterial in origin—in other words, if one is using cortisone for a condition which responds to this agent after long therapy—it may be that incidental bacteria will be multiplying which, when the action of cortisone is removed, will produce an unsuspected infection in the body. Unless the body is able to handle the infectious process by virtue of its natural resistance as enhanced by cortisone, the results of such therapy may be disastrous.

Antigen-Antibody Reaction—Immune Reaction

Because of the favorable reports in diverse clinical manifestations in man, such as urticaria, eczema, and diseases thought to have some allergic background, e. g., the collagen diseases, and in diseases such as uveitis, it becomes obvious that the

influence of these hormones on experimental antigen-antibody reactions should be studied. It has been shown by Woods [77g,p] and by Biegel [78k] that cortisone and corticotrophin will block the effects of an antigen-antibody reaction in ocular tissue brought about by horse serum or by bacterial sensitivity. Bennett and his co-workers [78l] demonstrated that both corticotrophin and cortisone exerted inhibitory effects on the development of the cardiovascular lesions of hypersensitivity, and the same group of workers demonstrated the favorable effect of cortisone on experimental cardiovascular and renal lesions produced by anaphylactic hypersensitivity. Others have made similar observations.[78n,o]

There are a number of workers who are unable to demonstrate that cortisone or corticotrophin could protect guinea pigs against anaphylactic shock.[78p-r] Nor was either substance able to modify the histamine shock, or passive or active anaphylactic shock.[78r] However, Harris and Harris did note suppression of manifestations of bacterial hypersensitivity.[78q]

Since cortisone or corticotrophin appears in some instances to influence the results of antigen-antibody reactions, the question arises: Does it influence the formation of antibody? The majority of investigators believe that there has been no significant influence on antibody formation. This has been demonstrated by Mirick,[78s] and Fischel,[78t] who have been able to induce antibody formation similarly whether cortisone or corticotrophin was used in patients following vaccination with pneumococcal polysaccharides. Production was exactly the same in patients treated with these agents as in those untreated. On the other hand, there is some evidence that antibody formation is suppressed. Germuth and Ottinger [78u] observed suppressed antibody formation to egg albumin with these agents, as did Roberts and White,[78v] and others. Bjørneboe and his co-workers [78w] noted the reduction in circulating antibody and in the lymphoid tissue when cortisone and corticotrophin were given, either at the beginning or after immunization was well advanced.

Influence of Cortisone or Corticotrophin on Enzymes

There is some evidence that these hormones interfere with the action of hyaluronidase and lysozyme, and stimulate the action of arginase and histamines.

Influence of Cortisone on Membrane Permeability

There is evidence that cortisone will decrease membrane permeability.[77t] However, local applications of cortisone to the eye failed to alter the permeability of the blood-aqueous barrier to the penetration of fluorescein from the blood stream.[77m] Menkin [78x] has demonstrated an increase in permeability with local cortisone suspensions, which, he believed, was due to the vehicle, and not to the cortisone itself.

Influence of Cortisone and Corticotrophin on Inflammatory Reactions Due to Chemical Irritants

It has been demonstrated by experiments of Jones and Myers,[79w,r] and by Woods and Wood [77p] that cortisone and corticotrophin will block the inflammatory reaction induced by chemical agents, such as alkali and jequirity. On the other hand, when the reactions are severe, such as those induced by turpentine [79n] and by concentrated alkali solutions,[77m] these agents fail to block the reaction. These studies suggest that cortisone works by virtue of concentration; when the irritant is very potent, the amount of cortisone available must also be great. The severer the inflammatory reaction, the more cortisone must be present to be effective.

Other Toxic Features

Other toxic features of local cortisone therapy which should be mentioned are atrophy of the skin with involution of the hair follicles, which may result from concentrated adrenocortical extract given percutaneously.[79b] These agents may produce hypersensitivity reactions. Antihistaminics may decrease the reaction.[79c]

A case of marked hyperlipemia from cortisone has been reported.[79d] This has also been shown to occur in rabbits receiving 7.5 mg. of cortisone, maintained on a balanced diet. In these animals there was a marked degree of hyperlipemia, with a rise in both the total fatty acids and the total cholesterol in the serum. A striking deposit of visible fat in the liver was observed. There was no constant parallelism between the degree of hyperlipemia and the degree of glycosuria.

Relationship of Ascorbic-Acid (Vitamin-C) Content of Adrenal Glands and the Adrenocorticotropic Hormones

The adrenal gland is unique in that it has one of the richest deposits of ascorbic acid of any organ. There is also a definite relation between the ascorbic-acid content of the adrenal and the adrenocortical-hormone concentration. It has been noted that on the administration of corticotrophin to rats there is a decrease in ascorbic-acid content of the adrenals.[83]

It is of interest to know whether there might be a decrease in synthesis of adrenal steroids under conditions imposed by deprivation of ascorbic acid. Both corticotrophin and cortisone prevent some of the manifestations of scurvy in small animals, according to Hyman and co-workers,[79g] and, according to Treager and his co-workers,[79e] adrenal cortex function in patients with scurvy is normal. It is evident from these reports that the presence of ascorbic acid in the adrenal gland is not necessary for manufacture of the adrenocortical steroid, although it should be recognized that the small amount of ascorbic acid that remains in the adrenals of scorbutic guinea pigs may be sufficient to carry out the synthesis.

Influence of Corticotrophin and Cortisone on Blood Coagulation

In experimental animals and in man, a variety of factors have been observed to induce changes in the coagulability of blood. Cannon had demonstrated that epinephrine when injected into experimental animals in small amounts accelerated clotting and materially delayed coagulation.[79h] This prolongation of clotting time with shock has been attributed to a circulating antithrombin. Evidence has been presented that the anticoagulant in anaphylactic shock is heparin, and that it is released from the mast cells. More recently, it has been demonstrated that similar changes occur in the mast cells of experimental animals receiving 11-dihydro-17-hydroxycorticosterone (cortisone). Selye has stated that the alarm reaction in general decreases the clotting time, and it is possible that the frequent occurrence of thrombosis following injuries or surgical procedures may be related to humoral factors released in response to stress. In man, disease with inflammation, necrosis, and thrombosis has been shown by Schilling and DeNatale[79i] to be accompanied with significant changes in the prothrombin time, which are not necessarily reflections of altered heparin levels. In the light of these observations, and on the premise that exogenous adrenocorticotropic hormone (corticotrophin; ACTH)

83. Treager, and others.[79e] Editorial.[79f] Steffensen.[77k]

induces some changes in the human being which qualitatively simulate a response to stress, Smith and his co-workers[79h] attempted to determine what effect these agents had on the coagulation mechanisms. Their results were not consistent from patient to patient. The alterations following the administration of these hormonal agents appeared to be in part a function of both the initial level of the adrenal cortex activity and the integrity of the coagulation mechanism itself which existed prior to the hormone administration. However, profound changes in coagulation time may follow administration of corticotrophin. As a rule, in the average patient, slight but significant lowering of clotting times occurs during therapy, with return to control levels when the hormone is withdrawn. There is little question that, though there are variations from patient to patient, adrenal cortex exerts an effect on the number of constituents in the clotting mechanism, and in some instances may alter significantly the clotting time when its function is accelerated.

The release of heparin or heparin-like substances into the blood following administration of corticotrophin and/or cortisone may be akin to the hyperheparinemia of anaphylactic shock. It affords an additional link in the present understanding of the interrelationship of the mast cells with production of heparin, the adrenal cortex, and the changes in blood coagulability which may accompany a response to stress.

Wound Healing

There is considerable evidence that cortisone will interfere with fibroblastic proliferation.[84] This interference apparently takes place in the early stages of formation of fibroblastic tissue, for once the fibroblastic tissue has formed cortisone or corticotrophin does not have a fibrolytic action[79j]; that is, these substances do not destroy the tissue which is already formed. It is apparent that this interference with healing bears some relation to dosage. The greater the concentration, the more likelihood of interference with healing of intraocular wounds; in low doses the effect may not be apparent, but in high doses the effect may be striking. This may be of considerable importance in the use of this agent after intraocular surgery. It may also be of practical value in the use of these agents in filtering operations, where excessive fibroblastic proliferation is undesirable. However, there is evidence that desoxycorticosterone acetate induces the production of an excessive amount of granulation tissue. This effect is more obvious if the desoxycorticosterone acetate is injected five days prior to operation, and is less obvious if it is given five days after operation. It also appears to encourage the deposition of homogeneous groundwork of collagen. Therefore, as cortisone depresses fibroblastic tissue early, and has no known fibrolytic activity late, so desoxycorticosterone acetate has action on immature proliferation connective tissue which is marked, but which is lessened or absent when the connective-tissue elements have reached partial, or almost complete, maturity.[79l,m] Cornman,[79n] however, was unable to demonstrate any effect of desoxycorticosterone acetate on fibroblast proliferation in tissue culture.

Relation to Fever Therapy

It has been known for some time, as a result of the work of Hartmann and Scott, in 1932, and of Edelson, in 1940, that adrenocortical extracts protect adrenalectomized rats against the lethal action of typhoid vaccine.[79o] Kass and

84. Leopold, and others.[77m] Spain, Mollomut, and Haber.[79j] Reagen, and others.[79k]

Finland [79p] demonstrated that the duration and intensity of the febrile reaction to bacterial pyrogen in the rabbit and in man are reduced by prior administration of corticotrophin. The mechanisms for this are unknown. Although the mechanism by which corticotrophin exerts its antipyretic effects is not clear, it is apparent that such an action of the hormone makes it possible that some patients will respond to the administration with reduction in fever but with no alteration of the fundamental pathologic processes of the illness being treated.

Arendshorst and Falls [79q] present data suggesting that successful foreign-protein therapy of ocular disease involves the release of 11,17-oxysteroids from the adrenal cortex. In their studies, maximal stimulation of adrenal cortex following the administration of typhoid H antigen was not reached for 18 hr., and single doses appeared to have a duration of action of approximately 24 hr. These workers believe that the intravenous injection of foreign protein initiates an alarm reaction, with the subsequent response to adrenal steroids, as shown by a decrease in eosinophils in the circulating blood. However, their results suggested that typhoid H antigen still has a place in the treatment of ocular disease. They suggest it as a supplementary therapeutic agent after withdrawal of corticotrophin from the patient and in cases in which a short course of elevation of the 11,17-hydroxysteroids will be effective in controlling the ocular disease. In such cases fever therapy will be helpful. However, whenever a more prolonged course is required, or when fever therapy does not give rise to a satisfactory eosinopenic response, the use of corticotrophin or cortisone should replace foreign-protein therapy. There is no doubt that fever therapy produces some of its results through this mechanism. However, we cannot be certain at present that this is the only mechanism by which fever therapy operates.

Relation of Autohemotherapy and Adrenocortical Stimulation

Autohemotherapy, that is, the intramuscular or subcutaneous injection of the patient's own freshly drawn venous blood, has been used by physicians for almost 40 yr. for many different diseases, either as sole treatment or as supplementary or complementary therapy. However, no objectively measurable physiologic therapeutic effect of autoblood has yet been demonstrated.

Saure [79r] presents evidence that autohemotherapy acts as a mild stimulant of the adrenal cortex. This is not to be accepted as proof that this is the only way in which the therapy works; it merely suggests it.

Other Steroids

Reports are beginning to appear in other fields of medicine concerning the use of other steroids in disease and their effects on normal physiologic activity. Studies with pregnenolone and progesterone have been made which show that these agents have the ability to inhibit the development of the chick embryo and to inhibit the development of estrogen-induced fibroma in guinea pigs. Progesterone proved to be one of the most potent of the steroids studied in this regard.[79s, t]

Other Hormones

The melanophore hormone of the pituitary has been tried in treatment of ocular disease.[79u-z] Corpus luteum hormone (progestin) has been tried in glaucoma.[79a']

It is evident that corticotrophin administered systemically, or cortisone administered systemically and/or orally, will block the manifestations of inflammatory reactions due to a variety of agents, such as the antigen-antibody reaction, bacterial infections, and chemical irritants. Although many mechanisms may be considered, the method by virtue of which these hormones produce this effect is not known. It is evident that corticotrophin has no local action but that cortisone has a definite local action. It is therefore unlikely that the systemic effects of cortisone, such as the influence on electrolyte balance, on carbohydrate and protein metabolism, on blood cells, or on blood elements, are the mechanisms for its blocking action in inflammatory changes. Certainly, the ability to tie up hyaluronidase, to decrease cell-membrane permeability, and to prevent cellular infiltration are important features, but whether they are the primary ones, or are secondary to some other action, is not known at present. It is extremely important to realize, as has been emphasized by almost all workers in this field, that any one using cortisone or corticotrophin understands that all he is doing with these agents is blocking the effect of disease. These agents do not attack the cause of the condition. They simply reduce the manifestations of the disease by the host. Let none of us be lulled into a sense of security by virtue of reduction in symptoms or signs with the use of these agents. Remember, we must find the cause of the disease whenever possible.

IRRADIATION AND RADIOACTIVE MATERIALS

Wilder and Maynard [85] have demonstrated the pathologic changes in experimental animal eyes that had received total body irradiation from atomic fission. These changes were similar to those from roentgen irradiation. For the most part, they may be regarded as the results of bone-marrow depression and secondary systemic changes, rather than the direct effect of the rays. Serous exudates occurred and are considered to be the result of increased vascular permeability, possibly secondary to anemia; the septic choroiditis is thought to be due to septicemia, and the massive cataract formation, to an irradiational, rather than a nutritional, effect. No ocular change noticed could be attributed unequivocally to direct irradiation.[86] Others have noted ocular changes produced by microwaves.[87] Most attention is paid to the cataract formations.

Friedell, Thomas, and Krohmer [88] have described an SR^{90} beta-ray applicator for ocular use. This applicator has been successfully employed in the treatment of superficial tumors of the eyelids and conjunctiva, vernal conjunctivitis, tuberculosis of the anterior segment, vascularization of the cornea, and corneal ulcers. Others have described additional experiences with beta irradiation of ocular

85. Wilder, H. C., and Maynard, R. N.: Ocular Changes Produced by Total Body Irradiation, Am. J. Path. **27**:1, 1951.

86. Lorenz, E., and Dunn, T. B.: Ocular Lesions Induced by Acute Exposure of the Whole Body of Newborn Mice to Roentgen Radiation, Arch. Ophth. **43**:742 (April) 1950.

87. Daily, L., Jr., and others: The Effect of Microwave Diathermy on the Eye, Am. J. Ophth. **33**:1241, 1950. Richardson, A. W.; Duane, P. D., and Hines, H. M.: Experimental Cataract Produced by Three-Centimeter Pulsed Microwave Irradiations, A. M. A. Arch Ophth. **45**:382 (April) 1951.

88. Friedell, H. L.; Thomas, C. T., and Krohmer, J. S.: Description of SR^{90} Beta-Ray Applicator and Its Use on the Eye, Am. J. Roentgenol. **65**:232, 1951.

conditions.[89] Ultrasonic waves can produce severe corneal damage.[90] Roentgen therapy may have benefit in ocular vaccinia [91] and in trachoma.[92] Katzin and Okrainetz [93] concluded from their observations that grenz rays are not effective in reducing the vascularization of corneas in rabbits. Krause and Bond [94] have shown that neutron and roentgen irradiation primarily damage the epithelial cells of the lens cortex, which, in turn, produces abnormal fibers leading to opacities in the subcapsular regions of the cortices. Neutron rays produce more damage per unit of absorbed energy than do roentgen rays.

It has been shown that the total body exposure to ionizing radiation suppresses the usual antibody response to antigens when these were injected shortly before or shortly after irradiation. This suppression has been attributed to the destructive effect of radiation on lymphatic tissue and bone marrow. Jacobson and his coworkers [95] studied the capacity of rabbits to form antibodies after the entire body, except the spleen or appendix, had been exposed to 800 r of roentgen radiation. It was demonstrated that if either the spleen or the appendix of the rabbit was protected by lead shielding during total body irradiation, the capacity to produce antibodies to an antigen was retained to a considerable degree, even though lymphatic tissue elsewhere in the body was temporarily destroyed.

Cataractous changes became demonstrable with the ophthalmoscope in 53 of 56 rabbits, four to 10 days after they received 2,000 r of penetrating roentgen rays.[96] The opacity started in the equator of the lens, then involved the posterior cortex, and then the anterior cortex, in characteristic pattern. There was some evidence of the direct effect of the radiation on the cytoplasm, as well as on the nuclei. Cytochemical studies indicated a definite change in the polymerization of desoxyribose nucleic acid, but it was not certain whether this was a primary change leading to nuclear degeneration or a change resulting from nuclear degeneration.

Radioactive tracers were employed to investigate the effect of roentgen irradiation on permeability of the lens and the blood-aqueous barrier. Although the permeability of the blood-aqueous barrier was increased, it did not seem to play an important role in the pathogenesis of radiation cataract. Some evidence is presented of increase in permeability of the cataractous lens. Experiments with radioactive indicators do not lend support to the theory that enhanced permeability

89. Swanbag, H.: A Radium Element Ophthalmic Applicator, Mississippi Valley M. J. **72**:68, 1950. Haik, G. M.: Beta Irradiation in Ophthalmology, New Orleans M. & S. J. **102**:504, 1950.

90. Olixia, E.: Action of Ultrasonic Waves on the Cornea of the Rabbit, Gior. ital. oftal. **3**:350, 1950.

91. Kline, O. R., Jr.: Roentgen Therapy of Ocular Vaccinia, Am. J. Ophth. **34**:342, 1951.

92. Redi, F.: Roentgen Contact Therapy on Treatment of Trachoma, Rass. med. sarda **51**:225, 1949.

93. Katzin, H., and Okrainetz, C.: Grenz Ray Irradiation of Vascularized Rabbit's Corneas, Am. J. Ophth. **33**:1904, 1950.

94. Krause, A., and Bond, J. O.: Neutron Cataracts, Am. J. Ophth. **34**:25, 1951.

95. Jacobson, L. O.; Robson, M. J., and Marks, E. K.: Effect of Roentgen Irradiation on Antibody Formation, Proc. Soc. Exper. Biol. & Med. **74**:145, 1950, cited in Postirradiation Antibody Formation, Editorial, J. A. M. A. **145**:906 (March 24) 1951.

96. von Sallmann, L.: Experimental Studies on Early Lens Changes After Roentgen Irradiation: I. Morphological and Cytochemical Changes, A. M. A. Arch. Ophth. **45**:149 (Feb.) 1951.

of the lens or the depressed processes of phosphorylation led to development of lenticular opacities from roentgen rays, but suggested, rather, that these changes accompany, and possibly influence, the progress of the opacification.[97]

Radioactive iodine has been used in the diagnosis and treatment of various types of thyroid dysfunction.[98] Radioactive iodine has both beta and gamma rays. The majority of the biologic activity is due to the beta particles, which are entirely absorbed within a distance of about 2 mm. of tissue. In fact, most beta rays travel less than 2 mm. Because beta radiation is absorbed so close to its source, intense local effects of irradiation occur whenever I^{131} is concentrated and is limited to this range. The gamma radiation penetrates, and much of it escapes the body. The effect of gamma rays is thus widely distributed. Consequently, the gamma effect in any medium is small. Since gamma rays escape in the body, this escape may be determined externally by the Geiger-Müller counter tube. The half-life of radioactive iodine is eight days. Thus, the radiation is limited to a relatively short period. It is a useful agent in diagnosis of thyroid function. The material is ingested, and then one measures the urinary excretion rate, the uptake of the radioactive material by the thyroid gland, and the incorporation in the hormonal iodine of the blood. It is used also in the treatment of hyperthyroidism and carcinoma of the thyroid.

Thiouracil and propylthiouracil are still very much in use in the treatment of thyrotoxicosis.[99] Taylor, Large, and Noth [99b] report a significant increase in exophthalmos in eight of 52 patients receiving propylthiouracil. There was no significant progression of exophthalmos in any case postoperatively. Definite regression following thyroidectomy occurred in four instances. These workers advise operation on all patients who are being given antithyroid drugs and show any tendency toward progressive exophthalmos.

Thorium X is a radioactive substance with a half-life period of 3,164 days. The remaining alpha particle is of such small penetrating power that when it is applied to the skin surface in alcoholic solution its effect is demonstrable beneath the

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97. von Sallmann, L., and Locke, B. D.: II. Exchange and Penetration of Radioactive Indicators in Normal and Irradiated Lenses of Rabbits, A. M. A. Arch. Ophth. **45**:431 (April) 1951.

98. Jaffe, H. L., and Otoman, R. E.: Radioiodine Test for Thyroid Function, J. A. M. A. **143**:515 (June 10) 1950. Schaffner, F.; Friedell, M. G., and Hummon, I. F.: Radioiodine (I^{131}) in the Diagnosis and Treatment of Diseases of the Thyroid, Illinois M. J. **99**:15, 1951. Clark, D. E.; Trippel, O. H., and Sheline, G. E.: Diagnostic and Therapeutic Use of Radioactive Iodine, A. M. A. Arch. Int. Med. **87**:17 (Jan.) 1951. Moe, R. H., and others: Evaluation of Radioactive Iodine in the Treatment of Hyperthyroidism, J. Clin. Endocrinol. **10**:1022, 1950. Haines, C. F.: Some Notes on the Role of Research in Development of Modern Treatment of Exophthalmic Goiter, ibid. **10**:989, 1950. Richards, C. E.; Crile, G., Jr., and McCullagh, E. P.: Radioactive Iodine in the Treatment of Hyperthyroidism of Nodular Goiter, ibid. **10**:1077, 1950. Shipley, R. A.; Storaasli, J. P.; Fredell, H. L., and Potts, A. M.: Radioactive Iodine in Diagnosis and Treatment of Hyperthyroidism, Am. J. Roentgenol. **64**:576, 1950. Weinbern, N.: Radioactive Iodine in Treatment of Thyroid Diseases, Review of Literature and Preliminary Report of Cases Treated, South African J. Clin. Sc. **1**:213, 1950.

99. (*a*) Greenburg, F. U., and Gruber, M.: Observations on Prolonged Medical Management of Toxic Diffuse Goiter with Thiouracil and Propylthiouracil, Am. J. M. Sc. **220**:373, 1950. (*b*) Taylor, N.; Large, A., and Noth, P.: Propylthiouracil in Thyrotoxicosis, ibid. **220**:362, 1950. (*c*) Bowers, R. E.: Treatment of Haemangiomatous Naevi with Thorium-X, Brit. M. J. **1**:121, 1951. (*d*) Bell, G. O., and Mishtowt, G. I.: Use and Abuse of Thiouracil Drugs, Am. J. Med. **10**:68, 1951.

surface for a distance of only 0.2 to 0.3 mm. Its effect is similar to that of a small dose of poorly penetrating x-rays. After repeated doses, short-lived vascular dilatation progresses to obliterative endangiitis. The thorium X is usually used in alcohol, 1,500 electrostatic units (E. S. U.) per millimeter. No more than 12 applications should be given.

Lorenz and Dunn [86] noted atrophy of the retina and lens and corneal opacities following the exposure of the entire body to radiant energy. They pointed out the relative high degree of sensitivity of young reticular and retinal tissues to radiant energy.

ULTRAVIOLET LIGHT

Ultraviolet light has many possible modes of action. It may be bactericidal, fungicidal, or virucidal. It may retard cell division or accelerate cell division. It may impair nitrogen metabolism, and it may impair carbohydrate uptake. It is said to cause some stimulation of muscle contraction, alteration of nuclear-membrane permeability, induction of chromosome abnormalities, alteration in permeability of cells, change of viscosity of fluids, and release of calcium. It may change proteins and may lead to the oxidation of proteins. Many possibilities are considered by Giese,[100] in a thorough review of the subject. It does seem, however, that visible light has the ability to reverse some of the effects of ultraviolet light.

Schwab and his co-workers [101] were able to show no essential difference between the action of low and that of high frequency rays on the cornea. Even radiation produced an exudate in the anterior chamber, whatever the frequency of the rays. Grun, Funder, and Wyt [102] were able to produce liquefaction of the vitreous and opacification in the lenses by the use of ultraviolet rays.

FEVER THERAPY

Many different bacteria, both pathogenic and nonpathogenic, produce pyrogens, substances which elevate the temperature of living tissue. Pyrogens are also physiologically effective on the circulatory system, on the endocrine glands, and on metabolic processes. They are frequently present in the form of contaminants of biologic materials, as they cannot be eliminated by conventional methods of cleaning or sterilization. It is generally held that bacterial pyrogens cause fever through an interfering action on the brain centers regulating body temperature. The latent period between injection and onset of fever does not suggest a direct action on centers, but indicates an intermediary mechanism, perhaps tissue injury.

The most potent pyrogens are produced by gram-negative bacteria, especially members of the coliform, Salmonella, and Pseudomonas groups. In these organisms, pyrogenic activity seems to be closely related to the somatic antigen. Pyrogens isolated chemically appear to be large, polysaccharoid molecules. They are relatively resistant to heat and are able to withstand autoclaving. The tolerance which some patients acquire to repeated injections of pyrogens is not related to humoral antibodies but may be due to an increased ability of the reticuloendothelial system to

100. Giese, A. C.: Action of Ultraviolet Radiation on Protoplasm, Physiol. Rev. **30**:431, 1950.

101. Schwab, F.; Wyt, L., and Nemetz, U. R.: Effect of Ultraviolet Rays on Anterior Segment of the Living Rabbit Eye, Klin. Monatsbl. Augenh. **116**:376, 1950.

102. Grun, C.; Funder, W., and Wyt, L.: Effect of Ultraviolet Rays on the Vitreous Body and the Lens, Klin. Monatsbl. Augenh. **116**:358, 1950.

remove the pyrogens from the circulation. The principal histologic change produced by pyrogens is widespread capillary damage. Injection of pyrogen is followed by striking changes in the circulating leucocytes and immediate leucopenic reaction, followed later by leucocytosis, an effect on the hemodynamics with a fall in blood pressure, and increase in renal blood flow. Numerous biochemical changes occur, such as depletion of liver glycogen. Doubtless, some of the effects of pyrogen are due to their stimulation of release of adrenal cortex hormones.[103]

Pyromen,* a pure carbohydrate derivative from a Pseudomonas species of bacterium, was discovered from observations of patients with chills and fever after intravenous administration of fluids, who appeared to be therapeutically benefited by these reactions. Since pyrogenic contamination is the commonest cause of chills and fever following venoclysis, and since fever has long been recognized as having therapeutic value, an effort was made to isolate the material responsible for these reactions, which led to the eventual preparation and standardization of pyromen.* Although the therapeutic value of this preparation was effective in suppressing the severity of chills, muscle ache and fever, the fact that allergic symptoms were sometimes temporarily accentuated after rather large doses limited the use of pyromen* to the treatment of asthma, dermatitis, uveitis, and other allergic syndromes. Later it became apparent that a satisfactory clinical response could be obtained with smaller doses, producing fewer, or no, constitutional symptoms.[104]

Randolph and his associates [104] suggest that the effect of pyromen* is evidently the result of stimulation of the pituitary-adrenal system, as has been suggested by Arendshorst and Falls.[79q] It is less effective than corticotrophin or cortisone, but is helpful particularly when combined with specific allergic therapy. Recommended single doses of this pyrogenic material vary from 0.5 to 10.0 γ. In this dose range, however, the febrile response is usually lacking.[104]

Pyromen,* supposedly, is not anaphylactogenic, and is antigenic only when increased amounts must be given for each succeeding bout, when repeated courses of fever are desired in a short period. When 25 γ, or 0.5 cc. of pyromen,* is given intravenously, the highest temperature recorded by Kierland and Kulwin [105] was 102.4 F. They have given injections as large as 125 γ or 2.5 cc.

Sentner [106] found that a mixture of 2.0 cc. of 4% procaine hydrochloride added to 9 cc. of milk enabled the injection to be made without the subsequent discomfort commonly experienced when milk alone is employed. The author found the two fluids to be miscible and compatible. When "pyrifer" was given in small doses, such as 10 units intravenously, to patients with inflammations of the conjunctiva, cornea, or iris, beneficial effects were obtained, although there were no febrile reactions. Spiecker [107] suggests that fever is not necessary to produce therapeutic effect.

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103. Bennett, I. L., and Bason, P. G.: Properties and Biologic Effects of Bacterial Pyrogens, Medicine **29**:365, 1950.

104. Randolph, T. P., and Rollins, J. P.: Pyromen in the Treatment of Perennial Allergic Symptoms, Ann. Allergy **8**:626, 1950.

105. Kierland, R. R., and Kulwin, M. H.: Clinical Evaluation of a New Pyrogenic Agent, Arch. Dermat. & Syph. **62**:571 (Oct.) 1950.

106. Sentner, J. A.: The Use of Milk Procaine in Foreign Protein Therapy, Am. J. Ophth. **33**:1437, 1950.

107. Spiecker, H. B.: The Therapeutic Effect of Minimal Doses of "Pyrifer" in Ophthalmology, München. med. Wchnschr. **92**:289, 1950.

FLUORESCEIN APPLICATIONS IN OPHTHALMOLOGY

The fact that diiodofluorescein is absorbed by tumors of the central nervous system has been utilized for localization of tumors. More recently, radioactive iodine I^{131} has been incorporated in the diiodofluorescein molecule, thus rendering the dye radioactive and permitting its detection through the bony cranium with a Geiger counter. The patient is given diiodofluorescein, containing 1.1 mc. of radioactive iodine, intravenously. Immediately after injection a shielded Geiger tube is placed over standard position, and counter and graphic recordings are begun immediately. In this manner one can determine the earliest time of relative stability of diiodofluorescein concentration. Once this stability is observed, the systematic survey of the cranium is begun. Since a contralateral composition for each position is important in the interpretation of the record, it is imperative that sites be alternated from side to side. Woolsey and Thoma present observations on 42 patients [108] examined with this test. Of these, 24 had normal records, and no evidence of tumor was listed by other methods of examination. Of the total of 17 positive positions, the correctness of the localization was proved in 9 by craniotomy or autopsy. To date, there has been no report of its trial in ocular tumors. When 2.0 to 3.0 cc. of 10% fluorescein sodium was injected intravenously, Offret and Caudin [109] noticed a pale, greenish coloring in the retinal film and accentuation of the retinal tear within seven to eight seconds. They state that fluorescein can help in localization of retinal tears that might not otherwise be recognized.

A method has been devised by Campbell and Boyd [110] using fluorescein for evaluating the rate of healing of corneal tissue. Oxygen deficiency has been found to increase the permeability of the blood-aqueous barrier to fluorescein.[111]

ANESTHESIA

There is evidence that solutions of histamine bichlorhydrate will inhibit cocaine anesthesia. It may be that this inhibition is due to the acidity and toxicity of the solutions.[112]

Procaine has little surface effect as an anesthetic. Anesthetics which work well when instilled into the eye, such as dibucaine, cocaine, and phenacaine, all inhibit cholinesterase. It has been shown that inhibitors of cholinesterase have increased the permeability of erythrocytes and the hemoencephalic barrier. If anesthetics with surface activity penetrate mucous membrane by virtue of their inhibitory action on cholinesterase, then nonsurface anesthetics might be made to be effective by the previous use of cholinesterase inhibitors, such as physostigmine. Grieg and co-workers [113] have shown this to be the case.

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108. Woolsey, R. D., and Thoma, G. E.: Localization of Intracranial Neoplasms with Radioactive Di-Idofluorescein, Missouri M. Soc. **47**:885, 1951.

109. Offret, G., and Caudin, A.: Can Fluorescein Help in the Diagnosis of Some Retinal Lesions? Bull. Soc. opht. France **2**:66, 1950.

110. Campbell, F. W., and Boyd, T. A. S.: Use of Sodium Fluorescein in Assessing the Rate of Healing in Corneal Ulcers, Brit. J. Ophth. **34**:545, 1950.

111. Giardini, A., and Swanlgung, H.: Effects of Anoxia on Fluorescein Permeability of the Blood-Aqueous Barrier, Brit. J. Ophth. **35**:114, 1951.

112. Jacob, J., and Rebass, L.: Inhibitory Action of Histamine Bichlorhydrate and of Acidity in Corneal Anesthesia in the Rabbit, Compt. rend. Soc. biol. **144**:920, 1950.

113. Grieg, M. B.; Holland, W. C., and Lindvig, P. E.: The Anesthetization of the Rabbit's Cornea by Nonsurface Anesthetics, Brit. J. Pharm. **5**:461, 1950.

Lidocaine (xylocaine®) hydrochloride has been shown to have many theoretical and practical advantages over procaine for regional anesthesia.[114] 1. It is stable in acid and alkaline solution and is not decomposed by boiling. 2. It has a slight vasoconstrictor effect—procaine is probably a vasodilator. 3. The absolute toxicity of xylocaine® is greater, but the relative toxicity is lower in that the dose required is clinically less. 4. Efficiency of xylocaine® in clinical doses is superior to that of procaine because (*a*) the time of onset is shorter, (*b*) the duration is longer, (*c*) intensity of anesthesia is longer, and (*d*) penetration is better and it diffuses more rapidly. 5. Xylocaine® is effective topically. 6. Xylocaine® works well without epinephrine. Doret[114b] uses a 2% solution for local and regional anesthesia. Four per cent xylocaine® hydrochloride is as effective a surface anesthesia as 2% cocaine.[114c]

Linn[115] analyzed 4,083 ophthalmic operations in which thiopental U. S. P. (pentothal®) sodium had been administered. About 4% of these patients experienced nausea and vomiting. An oral-pharyngeal airway was used in 72% of the patients, and the tongue was sutured in 4%. Fourteen patients died during the postoperative period, but only one death could be attributed positively to the anesthetic. The slow period of recovery would seem to be its chief disadvantage, according to Linn, because of the extra burden placed upon the nursing staff, it being necessary for the nurse to remain with the patient until recovery occurs.

Sanders and Cutler[116] analyzed the records of 62 patients with cataract operated on under general anesthesia. Cyclopropane-thiopental was the anesthesia employed. In four eyes complications developed because of postoperative vomiting. Parrish and co-workers[117] recommend use of vinyl ether (vinethene®) and ether with endotracheal intubation for ocular operations in which the eye is not opened.

WOUND HEALING

The influence of cortisone, corticotrophin, and desoxycorticosterone on wound healing is discussed under the section dealing with these hormones.

It has been suggested that ascorbic acid will favor the healing of deep corneal ulcers in man.[118] Heerema and Friedenwald[119] found that regeneration of corneal epithelium is greatly retarded by wool fat U. S. P., and that it is also retarded, but to a less degree, by petrolatum U. S. P. Campbell and his associates[120]

114. (*a*) Haglund, G., and Conroy, W. A.: Xylocaine for Regional Anesthesia, Illinois M. J. **99**:132, 1951. (*b*) Doret, M.: Xylocaine in Ophthalmology, Praxis **39**:491, 1950. (*c*) Bjorr, A.: On the Possibility of Testing the Surface Anesthetic Effect of Local Anesthetics on the Human Cornea, Acta ophth. **28**:229, 1950.

115. Linn, J. D.: Pentothal Sodium in Ophthalmic Surgery: 10 Year Review of its Use at Pittsburgh Eye and Ear Hospital, J. Internat. Coll. Surgeons **14**:453 (April) 1950.

116. Sanders, R. D., and Cutler, N. L.: General Anesthesia in Cataract Surgery, Arch. Ophth. **43**:653 (April) 1950.

117. Parrish, R. G.; Easton, E., and Karp, M.: General Anesthesia for Ophthalmic Surgery, Am. J. Ophth. **33**:383, 1950.

118. Boyd, T. A. S., and Campbell, F. W.: Influence of Ascorbic Acid on the Healing of Corneal Ulcers in Man, Brit. M. J. **2**:1145, 1950.

119. Heerema, J. C., and Friedenwald, J. S.: Retardation of Wound Healing in the Corneal Epithelium by Lanolin, Am. J. Ophth. **33**:1421, 1950.

120. Campbell, F. W.; Ferguson, I. B., and Garry, R. C.: Ascorbic Acid in Healing of Heat Injuries in Guinea Pig Cornea, Brit. J. Nutrition **4**:32, 1950.

have also indicated that vitamin C has no effect on the healing of superficial epithelial wounds, but has a definitely favorable influence on the regeneration of stroma, particularly in deep corneal wounds. It was evident that vitamin C-deficient animals showed a poorer regeneration of deep corneal wounds than did those with adequate vitamin-C intake.

There is further evidence that the antibiotics in recommended concentrations do not interfere significantly with epithelial regeneration in experimental animal eyes.[121] High concentrations of penicillin, of the order of 50,000 units of penicillin G per cubic centimeter, and of bacitracin, 1,000 units per cubic centimeter, have been found to retard epithelial regeneration. This confirms the earlier work of Locke [122] and of Bellows and Farmer.[123] Local anesthetics and detergents were found to retard epithelial regeneration, as has been reported previously.[26d]

Cruithird [124] continues to describe the beneficial effect of sulfhydryl compounds on clinical chemical burns of the eye. Topical application of a 5 to 10% aqueous solution of acetylcholine instilled every five to 10 min. during the acute stages of a burn reduced the amount of permanent tissue damage.[125]

Since there is evidence that circulation of fluid through the cornea starts at the limbus and spreads to the aqueous humor posteriorly, and to the tears anteriorly, Novakovic [126] recommends the use of hypertonic salt or sugar solutions for acceleration of circulation in cases of corneal lesions. Two to 4% sodium chloride solutions were employed locally. Friede [127] employed a 40% dextrose ointment, powdered glucose, as well as hypertonic solutions. These were often combined with antibiotics.

Evidence has been presented that p-aminobenzoic acid has a favorable action both on the process of reepithelization and on regenerative processes of the connective tissue.[128]

Schaeffer [129] has demonstrated that amino acids accelerated the healing of abraded corneas. The most important of these was cystine, because of its thiol (SH) content.

Blocking of the stellate ganglion does not modify the course of superficial corneal ulcers, and retrobulbar injections of procaine failed to help the healing of corneal burns.[130]

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121. Marr, W. G.; Wood, R., and Storck, M.: The Effect of Some Agents on Regeneration of Corneal Epithelium, Am. J. Ophth. **34**:609, 1951.

122. Locke, J. C.: Experimental Studies with Antibiotics, Am. J. Ophth. **32**:135, 1949.

123. Bellows, J., and Farmer, C. J.: The Use of Bacitracin in Ocular Infections, Ann. Ophth. **31**:1070 and 1211, 1948.

124. Cruithird, A. E.: The Use of Sulfhydryl in the Treatment of Scars Following Chemical Eye Burns and Ulcers, Tr. Am. Acad. Ophth. 32, 1950.

125. Haselmann, G., and Pulfrich, K.: Treatment of Burns with Acetylcholine, Ophthalmologica **120**:381, 1950.

126. Novakovic, A.: Therapeutic Effects of Hypertonic Solutions on the Cornea, Voj. san. pregl. **7**:159, 1950.

127. Friede, R.: Present Position of Glucose Therapy in Ophthalmology, von Graefes Arch. ophth. **150**:645, 1950.

128. Bonaccorsi, A.: The Effect of P-Aminobenzoic Acid on Experimental Lesions of the Cornea, Minerva chir. **5**:275, 1950.

129. Schaeffer, A. J.: An Attempt to Influence Corneal Wound Healing by Local Application of Certain Amino Acids, Am. J. Ophth. **33**:741, 1950.

130. Pinto, S. P.: Corneal Ulcers and Blocking of the Sympathetic, Arch. Portug. oftal. **2**:47, 1950.

PREPARATION OF OPHTHALMIC SOLUTIONS

Martin and Mims [131] state that any solution to be instilled in the conjunctival cul-de-sac which has a tonicity equivalent to that of 0.9 to 1.4% solution of sodium chloride is acceptable—that its pH should be between 4.5 and 4.9. Isotonic phosphate-buffered solutions do not produce any unpleasant sensation in the majority of eyes when instilled if the pH is between 6.6 and 8.7. However, any combination of ions and substances in solution should be tested for the proper pH. Attention should be directed to the stability of the drug in solution and in the vehicles usually employed. From the standpoint of stability of atropine, pH 7 is optimal.[132] Schaeffer [133] has also reviewed the many features involved in local ocular therapy.

ANTICOAGULANTS

Heparin can be used in several ways: intravenously, either intermittently, in a dose of 50 to 150 mg., or continuously, in a concentration of 300 to 500 mg. per 1,000 cc. of diluent. It can also be administered intramuscularly, as a 5 or 10% aqueous solution. A repository form is available, which can be administered either subcutaneously or intramuscularly. By virtue of the vehicle, heparin absorption can be retarded so that the action of the drug is spread over 12 to 48 hr. To determine the proper dose, one should determine the coagulation time before starting treatment. If one plans to use a repository product, tests should be made every 12 hr. the first day, after a 24-hr. interval on the second day, and at 24-hr. intervals thereafter. In prophylactic therapy one should strive for a clotting time which is at least twice, or, better still, three times, the control value.[134] The Lee-White modification of the Howell method can be used for these measurements.[135] Most ambulatory patients will require between 100 to 300 mg. every 24 to 48 hr. The purpose of such prophylactic therapy is to correct the tendency to hypercoagulability, which may be responsible for intravascular clotting.[136]

New drugs are appearing in the coumarin series, such as tromexan® (ethyl bis [4-hydroxy-2-keto-3-a-benzopyramyl] acetate). This drug supposedly has a more

131. Martin, F. N., Jr., and Mims, J. L.: Preparation of Ophthalmic Solutions with Special Reference to Hydrogen Ion Concentration and Tonicity, Arch. Ophth. **44**:561 (Oct.) 1950.

132. Kebvessy, G.; de Grosz, S., and Szepesy, A.: Preparation of Ophthalmic Solutions, Brit. J. Ophth. **34**:228, 1950.

133. Schaeffer, A. J.: Some Aspects of Ocular Pharmacology, Docum. ophth. **4**:227, 1950.

134. Loewe, L.; Berger, L., and Lasser, R.: Prevention of Thromboembolism, Angiology **2**:26, 1951.

135. Olwin, J. H.: The Significance of Different Methods of Prothrombin Estimation and Their Relative Values, Surg., Gynec. & Obst. **90**:423, 1950.

136. Loewe and others.[134] Bauer, G.; Boström, H.; Jorpes, E., and Kallner, S.: Intramuscular Administration of Heparin, Acta med. scandinav. **136**:188, 1950. Bauer, G.: Nine Years' Experience with Heparin in Acute Venous Thrombosis, Angiology **1**:161, 1950. Smiles, W. J.: Long-Acting Heparin Preparation: A Useful Adjunct in Anticoagulant Therapy, U. S. Armed Forces M. J. **2**:45, 1951.

rapid effect than dicoumarin (dicumarol®) on the prothrombin time. Single doses act only 24 hr. This is probably an advantage over dicoumarin.[137]

Tromexan® prolongs the prothrombin time and has about one-fifth the potency of dicoumarin in terms of effect on prothrombin time. It has a faster rate of absorption and utilization than dicoumarin. Its duration of effect is about one-fourth that of dicoumarin. Satisfactory maintenance of a therapeutic level of hypoprothrombinemia can be achieved by a single daily dose of 600 to 2,400 mg., or by 300 to 900 mg. in two to three divided doses.[138]

Of the many complications which may result from this therapy, death is an outstanding one. Deaths are still being reported. Deaths occurred in four patients treated with dicoumarin who were adequately studied.[138] It was thought that these deaths may have occurred because of unreliable laboratory tests, as the prothrombin time of three of these patients ranged from 33 to 40% and that of one was 25 to 33% of normal. It is important to keep in mind that other drugs, e. g., p-aminosalicylic acid, will cause prolongation of the prothrombin time.[139]

De Takats[140] showed that an emulsion of heparin in gelatin as a retarding medium served as a simple and efficient anticoagulant when injected subcutaneously. The great variability of response to heparin makes set schedules of dosage impossible. Two milligrams per kilogram of body weight is a good average prophylactic dose. The administration of heparin should be continued for two weeks in the case of an acute thromboembolic episode.[139]

Intoxication with dicoumarin may be manifested by bleeding, probably because of the production of hypoprothrombinemia. James[141] has seen hemorrhage without there being a very pronounced alteration of prothrombin time. He has observed many other patients whose prothrombin time was exceedingly low and who did not bleed. Other factors must play a part, such as the vascular status, trauma, and the state of nutrition. Best results are obtained in control of hemorrhage by use of over 500 mg. of vitamin K_1 oxide intravenously.

Larsson and Nord[142] reported treatment in 100 cases of retinal-vein thrombosis—41 cases of contributory and 59 cases of central-vein thrombosis—with heparin and dicoumarin. They were not impressed with the results.

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137. (*a*) Hausner, E. P., and others: Clinical Evaluation of Dicumerinyl Derivatives with a Metabolic Study of the Radioactively Labeled Anticoagulants in Animals, Circulation **3**:171, 1951. (*b*) Burke, G. E., and Wright, I. S.: Tromexan (3,3'-Carboxymethylenebis [4-Hydroxycoumarin] Ethyl Ester): Experimental and Clinical Properties, ibid. **3**:164, 1951. (*c*) Blaustein, A. B.; Croce, J. J.; Alberrian, N., and Richey, N.: A Preliminary Report on Clinical Use of a New Anticoagulant, Phenylindandione, ibid. **1**:1195, 1950. (*d*) Sorenson, C. W.; Seifter, J., and Wright, I. S.: New Synthetic Anticoagulant (Heparinoid), Bull. New York Acad. Med. **25**:448, 1950.

138. Wright, L. T., and Rothman, N.: Deaths from Dicumarol,® A. M. A. Arch. Surg. **62**:23 (Jan.) 1951.

139. Lynch, M. J. G.: Effect of Para-Aminosalicylic Acid on Prothrombin Time, J. Clin. Path. **3**:114, 1950.

140. de Takats, G.: Subcutaneous Use of Heparin, Circulation **2**:837, 1950.

141. James, D. F.: Practical Aspects of Treatment of Dicumarol Intoxication, J. Georgia M. A. **40**:8, 1951.

142. Larsson, S., and Nord, B.: Remarks on Retinal Vein Thrombosis and its Treatment with Anticoagulants, Acta ophth. **28**:187, 1950.

Failures in anticoagulant therapy [143] can be attributed to (1) late onset of therapy; (2) failure to maintain effective levels, and (3) premature discontinuance of therapy. Anyone using anticoagulants must have (1) an adequate method and competent technicians for determining prothrombin times; (2) knowledge of contraindications, e. g., hypoprothrombinemia associated with liver disease, vitamin-K and vitamin-C deficiency, blood dyscrasias, and renal insufficiency; (3) knowledge of the effect of other drugs, as noted above (salicylates enhance the activity of coumarin derivatives; corticotrophin and cortisone may increase the tendency to thrombosis); (4) interest in the new anticoagulants, such as paritol [143] (derivative of polyanhydromannuronic acid), similar to heparin in action, tromexan,® [137b] and phenylindandione.[137c]

AUTONOMIC DRUGS

Acetylcholine is apparently formed from relatively inactive choline. Nachmansohn and Machado, in 1943, reported on the enzyme choline-acetylase, which is capable of synthesizing acetylcholine in vitro. This enzyme has been demonstrated in nerve- and muscle-containing tissues of many animals. It was demonstrated in tissues that have been known to possess cholinesterase.

deRoetth [144] has shown that choline acetylase exists in the iris, ciliary body, and retina of the rabbit and the cat eye. Feldberg [145] has shown that the retina contains large amounts of choline acetylase, and that the optic nerve is free from it. This suggests that the optic nerve is noncholinergic. From evidence presented by Feldberg and associates,[146] it is possible that the first neuron of the retina, the rods and cones, may be noncholinergic, and the second neuron, cholinergic. The third neuron, the optic nerve, is also noncholinergic, and the fourth neuron, the lateral geniculate body, cholinergic.

Acetylcholine is thought to be the chemical substance responsible for the transmission of impulses across synapses throughout the nervous system, and it is responsible for activation of all structures supplied by the parasympathetic nervous system and the voluntary motor system. Acetylcholine may cause contraction, compression, or contracture of a muscle.[145] In small doses it causes contraction; in large doses depression may follow contraction. This depression can be explained by either prolonged persistence of acetylcholine at the end-plate region or, more likely, by depolarization extending beyond this region to the muscle fiber. Depolarization of a muscle fiber blocks transmission; depolarization of the end plate causes an excitation wave.[145] This ability of acetylcholine in larger doses to cause depression of response may be of practical importance. This may mean that combinations of cholinergic drugs, or cholinergic drugs plus anticholinesterase agents, allowing large accumulations of acetylcholine, may lead to a depression of desired effect in diseases such as glaucoma, rather than an increased activation.

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143. Wright, I. S.: Use and Abuse of Anticoagulant Drugs in Clinical Practice, Pennsylvania M. J. **54**:313, 1951.

144. deRoetth, A.: Choline Acetylase Activity of Ocular Tissue, Arch. Ophth. **43**:849 (May) 1950.

145. Feldberg, W.: Role of Acetylcholine in Central Nervous System, Brit. M. Bull. **6**:312, 1950.

146. Feldberg, W.; Harris, G. W., and Linn, R. C. Y.: Observations on the Presence of Cholinergic and Noncholinergic Neurons in the Central Nervous System, J. Physiol. **1**:124, 1951.

It is well known that the enzyme capable of hydrolyzing the acetylcholine rapidly that is found in the tissues is cholinesterase. The cholinesterase that exists in the tissue is varied, consisting of specific and nonspecific varieties.[147] The nonspecific cholinesterase is probably not materially concerned in the neurohormone function. The specific cholinesterase has a high affinity for acetylcholine. It must be remembered that in all tissues, or in any given tissue, there may be several existing cholinesterases. However, usually one type predominates. These types of cholinesterases differ in response to drugs. For example, diisopropyl fluorophosphate inactivates nonspecific cholinesterases in concentration much lower than that required for inhibition of specific cholinesterase.

deRoetth[148] has recently determined the cholinesterase activity in ocular tissues of many animal eyes, and in the human eye. The highest cholinesterase activity was found in muscle- and nerve-containing tissues, that is, the iris, ciliary body, and retina. The aqueous and vitreous contained only traces of this enzyme. The retina of almost all species studied had approximately the same enzyme activity, but the irides and ciliary bodies varied considerably in their exact content from one species to another.

deRoetth[148] was able to correlate the degree of cholinesterase activity in the iris and ciliary body with the amount of muscle tissue present in the structure. Very high concentrations of specific cholinesterase were found in the ciliary body, as great as 10 times that found in the iris. The extraocular muscles also have a high concentration of cholinesterase. It is interesting to note that in eyes with absolute glaucoma there was definite reduction of the concentration in the ciliary body and in the iris, but this did not differ significantly from that found in globes degenerated for reasons other than high intraocular pressure.

Feldberg[145] has demonstrated that nerve trunks have a high cholinesterase content, but this is not a universal finding. Koelle and others[149] have demonstrated that the concentration in the synaptic region is usually higher than it is in the nerve fibers.

Grant[150] and Marr and Grob[151] have demonstrated that tetraethylpyrophosphate, an anticholinesterase agent, is able to lower intraocular pressure in glaucomatous eyes. It is apparent that its practical value is limited because of the frequency of sensitization to the agent.

Both tetraethylpyrophosphate and octomethyl pyrophosphoramide have been shown to have benefit in myasthenia gravis, as discussed elsewhere in this review.

Mintacol (diethoxyphosphor acid-p-nitrophenol ester) is pharmacologically related to diisopropyl fluorophosphate. It has some success in cases of glaucoma

147. Koelle, G.: Histochemical Differentiation of Types of Cholinesterases, and Their Location in Tissues of the Cat, J. Pharmacol. & Exper. Therap. **100**:58, 1950. Koelle, G. B., and Koelle, E. S., and Friedenwald, J. S.: Effect of Inhibition of Specific and Nonspecific Cholinesterases on the Motility of the Isolated Ileum, ibid. **100**:180, 1950.

148. deRoetth, A., Jr.: Cholinesterase Activities in Ocular Tissues and Fluids, Arch. Ophth. **43**:1004 (June) 1950.

149. Koelle and others.[147] Koelle, G. R., and Friedenwald, J. S.: Histochemical Localization of Cholinesterase in Ocular Tissues, Am. J. Ophth. **33**:253, 1950.

150. Grant, W. M.: Additional Experiences with Tetraethylpyrophosphate in Treatment of Glaucoma, Arch. Ophth. **44**:362 (Sept.) 1950.

151. Marr, W. G., and Grob, D.: Some Ocular Effects of a New Anticholinesterase, Am. J. Ophth. **33**:904, 1950.

in an aqueous solution of 1:6,000 concentration.[152] Alcohol has a slight influence on cholinesterase.[153]

SYMPATHETIC-NERVE HORMONE

There has been considerable discussion in the literature for years as to the exact nature of the chemical substance liberated at the endings of the postganglionic sympathetic fibers after stimulation. At various times it has been suggested as being epinephrine, or a combination of sympathin I and E, or nor-epinephrine, also called "arterenol." It has been suggested that nor-epinephrine produces activity at the end organs of part of the sympathetic system, and that epinephrine is responsible for inhibitory, as well as stimulatory, effects on the end organs supplied by the postganglionic fibers in the sympathetic system. Thus, the tendency at present is to abandon the idea that epinephrine combines with hypothetical sympathin to produce sympathin E and I.[154] It has been demonstrated again that the degeneration of the sympathetic nerve results in increased sensitivity of smooth muscle to epinephrine, especially after postganglionic, as compared with preganglionic, section of the nerve.[155]

Nor-epinephrine is more prominent in adrenergic nerves than epinephrine, and von Euler[154] believes that it is a dominant adrenergic neurohormone. Langemann[156] believes that nor-epinephrine is formed from dihydroxyphenylalanine, called D. O. P. A., by decarboxylase enzymes, yielding hydroxytyramine, and this is transformed into nor-epinephrine. Nor-epinephrine can be inactivated by aminoxidase and by catechol oxidase. Von Euler[154] suggests that nor-epinephrine is a sympathetic neurohormone for general service, but epinephrine acts as an adjuvant for more special purposes, especially as regards metabolic action. Nor-epinephrine is found throughout the body; only the placenta and bone marrow appear to lack some nor-epinephrine content. Humphreys and Raab[157] have demonstrated that nor-epinephrine is but one-sixth as potent as epinephrine in liberating cortical hormones. It appears that methionine has a definite effect on the methylation of nor-epinephrine.[158]

If the nictitating membrane of the cat is denervated, it is possible to demonstrate a difference in the degree to which this membrane is sensitized to various sympathomimetic amines. For example, after preganglionic denervation, ephedrine, tyramine, amphetamine, and β-phenylethylamine produce only a twofold to threefold increase in sensitivity reaction, whereas epinephrine and nor-epinephrine are associated with

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152. Neuenschwander, M.: Mintacol Bayer: A New Antiglaucomatous Drug, Ophthalmologica **120**:104, 1950.

153. Todrick, A.; Fellowes, K. S., and Rutland, J. P.: The Effect of Alcohol on Cholinesterase, Biochem. J. **48**:360, 1950.

154. von Euler, U. S.: Hormones of the Sympathetic Nervous System and the Adrenal Medulla, Brit. M. J. **1**:105, 1951.

155. Judson, W., and others: Hemodynamic Response of Intravenous Epinephrine, J. Clin. Invest. **29**:1405, 1950.

156. Langemann, H.: Abstract, Comm. 18th International Congress of Physiologists, Copenhagen, 1950.

157. Humphreys, R. J., and Raab, W.: Influence of Noradrenalin on Cortical Hormones, Proc. Soc. Exper. Biol. & Med. **74**:302, 1950.

158. Hutcheon, D. E., and Parker, R. H. O.: The Effect of Methionine on the Methylation of Noradrenalin in the Body, Brit. J. Pharmacol. **5**:604, 1951.

a sevenfold increase in threshold sensitivity. After postganglionic sensitization, there is a decreased sensitivity of the end organ to β-phenylethylamine, ephedrine, tyramine, and amphetamine, whereas there is a sevenfold increase in sensitivity to epinephrine and a 20-fold increase to nor-epinephrine.[159] On the other hand, there is some evidence arguing against the role of nor-epinephrine in autonomic transmission of nerve impulses. For 15 min. after stimulation of the splanchnic nerve, only epinephrine is detected in the plasma of the adrenal vein.[160] There is evidence that nor-epinephrine is the precursor of epinephrine.[161] Van Arman[162] found that a complete diet of an amino-acid mixture, or dehydroxyphenylalanine, appeared to be necessary for the formation of epinephrine. Considerable evidence is available demonstrating the differences in action of epinephrine and nor-epinephrine.[163]

Lockett demonstrated the differences of tissue response to epinephrine tyramine, phenylalanine, and amphetamine.[164] It has been demonstrated by Cannon that intravenous or subcutaneous injections of small amounts of epinephrine could shorten the coagulation time of blood.

Adrenoxyl is the monosemicarbazone of adrenochrome. Adrenochrome results from oxidation of epinephrine. Adrenochrome is hemostatic but is not easily preserved. Adrenoxyl is a stable, synthetic compound that has hemostatic action, like that of epinephrine, but does not produce sympathomimetic effects. One hundred to 500 γ of adrenoxyl in normal adult males produced no change in pulse rate, respiratory rate, blood pressure, pupillary reaction, or clotting time. Adrenoxyl produces a decrease in bleeding time of dog and man; 30 to 60 γ must be given for minimal effect.[165]

A disturbance in distribution of acute catechol amines is encountered in connection with various endocrine disturbances, such as posthypophysectomy, thyrotoxicosis, and post-thyroidectomy states. This applies to the adrenal medulla, and other organs as well. For example, the rat spleen after hypophysectomy shows an increased content of epinephrine; after thyroidectomy the epinephrine content is decreased. A large field is opening up in this connection which may be of

159. Lockett, N. F.: Effect of Denervation on the Responses of the Cat's Nictitating Membrane to Sympathomimetic Amines, Brit. J. Pharmacol. **5**:485, 1950.

160. West, G. P.: Liberation of Adrenalin from the Suprarenal Gland of the Rabbit, Brit. J. Pharmacol. **5**:542, 1950. Brown, J. H.; Hutcheon, D. E., and Parker, R. H. O.: Suprarenal Extracts After Insulin, ibid. **5**:417, 1950.

161. Blashko, H.; Burn, J. H., and Langemann, H.: Formation of Noradrenalin, Brit. J. Pharmacol. **5**:431, 1950. West, G. B.: Further Studies on Sympathin, ibid **5**:165, 1950.

162. van Arman, C. G.: Amino Acids and Amines as Precursors of Adrenalin, Am. J. Physiol. **164**:476, 1951.

163. De Largy, C.; Greenfield, A. M.; McCrorry, C. L., and Whelan, R. F.: Effects of Intravenous Infusion of Mixtures of l-Adrenalin and l-Noradrenalin on the Human Subject, Clin. Sc. **9**:71, 1950. Barnett, A. J., and others: The Action of Noradrenalin in Man and Its Relation to Pheochromocytoma and Hypertension, ibid. **9**:151, 1950. Blacket, A. B.: Bickering, T. W., and Wilson, G. N.: Effects of Prolonged Infusions of Noradrenalin and Adrenalin on Arterial Pressure of the Rabbit, ibid. **9**:247, 1950. Swan, H. J.: Observations on the Central Dilator Action of Adrenalin in Man, J. Physiol. **112**:426, 1951.

164. Lockett, N. F.: Responses to Sympathomimetic Amines, J. Physiol. **111**:19, 1950.

165. Hagerty, R. F.; Zavertnick, J. J., and Grimson, K. J.: Effect of Adrenoxyl on Blood Loss from Surgical Wounds, A. M. A. Arch. Surg. **62**:420 (March) 1951.

interest for interpretation of certain vegetative disorders in connection with hormonal imbalance.

Brown [166] was unable to find any evidence of sympathetic innervation of the extrinsic ocular muscle. It has been demonstrated that after denervation of sympathetic ganglia in the cat there is reduced formation of acetylcholine, and that this reduction in formation can be correlated with the loss of choline acetylase.[167]

Epinephrine ascorbate may be useful in treatment of chronic glaucoma, hypertensive uveitis, and allergic eczema of the eyelids. This compound is well tolerated and is effective.[168]

ADRENERGIC BLOCKING AGENTS

An adrenergic blocking agent is one which specifically inhibits certain responses of effector cells to epinephrine, related amines, and sympathetic-nerve impulses.[169] There are many agents with adrenergic blockade effects. Dibenamine® is a type of β-haloalkylamine and represents one of the most recently discovered series of adrenergic blocking agents. Other agents are the ergot alkaloids, the imidazolines, the benzodioxans, and the yohimbines. Additional evidence has been presented by Newell and co-workers,[170] Clark and Duggan,[171] Mullen and Leopold,[172] Bloomfield and Haimovici,[173] Posner,[174] and DeLong and Scheie [175] that dibenamine® is able to reduce intraocular pressure in eyes with glaucoma. The best results were obtained in eyes with acute forms of glaucoma, either of acute primary type or that following uveitis. Evidence has also been presented that other adrenergic blocking agents, such as the ergot alkaloids,[176] will successfully lower intraocular pressure. These data confirm the initial impressions of Thiel, in 1926, and Swann, Christensen, and Gould, in 1948.

Dibenamine® and ergot alkaloids appear to be active in atropinized eyes, and in eyes in which they produced no noticeable effect on the size of the pupils, such as in iris bombé. It may have a tension-lowering effect through its action on the formation of intraocular fluids. This effect is not due to the influence on the general blood pressure. It is probably not due to peripheral vasodilatation, as those

166. Brown, G. L.: Sympathetic Innervation of the Extrinsic Ocular Muscles, J. Physiol. **112**:211, 1951.

167. Bannister, J., and Scrase, N.: Acetylcholine Synthesis in Normal and Denervated Sympathetic Ganglion of the Cat, J. Physiol. **111**:437, 1950.

168. Voisin, M., Favert, and Toxcin: A New Adrenalin Derivative Used in Conjunctival Instillation, Bull. Soc. opht. Paris, 1950.

169. Nickerson, M.: Pharmacology of Adrenergic Blockade, J. Pharmacol. & Exper. Therap. **95**:27, 1949.

170. Newell, F. W.; Ridgway, W. L., and Zeller, R. W.: Dibenamine in Glaucoma, Am. J. Ophth. **34**:527, 1951.

171. Clark, W. B., and Duggan, J. W.: Dibenamine in Acute Congestive Glaucoma, ibid. **34**:535, 1951.

172. Mullen, C., and Leopold, I. H.: Experiences with Dibenamine in Glaucoma, read before the Third Clinical Conference of the Wills Hospital, March 16, 1951.

173. Bloomfield, S., and Haimovici, H.: Effect of Dibenamine® in Chronic Simple Glaucoma, Arch. Ophth. **43**:969 (June) 1950.

174. Posner, A.: The Effect of Certain Hydrogenated Alkaloid Ergot on Glaucoma, Am. J. Ophth. **33**:1551, 1950.

175. DeLong, S., and Scheie, H. G.: Actions of Dibenamine,® read before the College of Physicians, Philadelphia, Section on Ophthalmology, April 19, 1951.

176. Mullen and Leopold.[172] Posner.[174]

agents such as priscoline® (benzazoline), which bring about more pronounced dilatation, are not as effective. Dibenamine® and other adrenergic blocking agents have disadvantages. These agents produce some undesired effects through their action on the cardiovascular system and on the central nervous system. Their action is only temporary; and unless some surgical procedure or other form of therapy is instituted, the benefit obtained from the adrenergic blocking agents will not persist.[177] At present, oral administration of these agents has not been very successful in the treatment of glaucoma. The problem is still one for further investigation.

Considerable work is being done with these agents in the control of blood pressure.[178] Hydergin, which is a mixture of equal amounts of three hydrogenated alkaloids of the ergotoxin group, is said to have less symptomatic effect, that is, to produce less nausea, vomiting, and headache, than dihydroergocornine. However, it is said that hydergin retains the other properties, of vasodilatation, epinephrine reversal, etc.[178a]

Priscoline® (2-benzyl-4,5-imidazoline hydrochloride), which is an adrenergic agent, as well as an autonomic-ganglion-blocking agent, was shown by Lynn and others[179] to be of value in the treatment of vasospastic disorders, but it is unlikely that it will benefit patients with occlusive vascular disease. It may be of value in determination of suitable candidates for sympathectomy.

Preliminary data suggest that C6 may be used clinically in evaluation of sympathetic vasoconstrictor component in cases of peripheral vascular disease, as well as in the treatment of acute peripheral vascular disorders associated with neurogenic vasospasm.[180] Alve[181] has shown that dibenamine® may have a double

177. Newell and others.[170] Clark and Duggan.[171] Mullen and Leopold.[172] Bloomfield and Haimovici.[173] Posner.[174] DeLong and Scheie.[175]

178. (*a*) Barcroft, H.; Konzett, H., and Swan, H. J. C.: Observations on the Action of a Hydrogenated Alkaloid of the Ergotoxin Group in Circulation of Man, J. Physiol. **112**:273, 1951. (*b*) Freis, E. D.; McKay, J. C., and Oliver, W. F.: Effect of Sympatholytic Drugs on the Cardiovascular Responses to Epinephrine and Norepinephrine in Man, Circulation **3**:254, 1951. Prunty, F. T. G., and Swan, H. J. C.: Action of Benzodioxane in Man, Lancet **1**:759, 1950. Gretz, R. H.: Effect of Sympatholytic Drugs on the Cardiovascular System in Man, with Special Reference to Hypertension, Angiology **2**:1, 1951. Chen, G., and Russell, B.: Antagonistic Action of Adrenergic Blocking Agents on Vasopressor Effect of Epinephrine, Arch. internat. pharmacodyn. **84**:176, 1950. Chen, G.; Nash, V. L., and Russel, B.: Evaluation of Adrenergic Blocking Agents, ibid. **84**:269, 1950. Kappert, A., and Hadorn, W.: Experimental and Therapeutic Investigations with Certain New Hydrogenated Ergot Alkyloids in Peripheral Vascular Disorders, Angiology **1**:520, 1950. Josephs, I. L.: Therapy of Hypertension: Use of Veratrum Veride Alone and Combined with Certain Dihydrogenated Alkaloids of Ergot, Ann. West. Med. & Surg. **4**:789, 1950. Nuzum, F. R.: Dihydrogenated Ergot Alkaloids in Treatment of Essential Hypertension, ibid. **4**:781, 1950. Thorner, M. C.; Stoplstad, C. T., and Griffith, G. C.: Effect of Dihydrogenated Ergot Alkaloid CCK-179 on Electrocardiograms, ibid. **4**:795, 1950. Trapold, A. H.; Warren, M. R., and Woodbury, R. A.: Pharmacological and Toxicological Studies on C7337 (Aninemadazline): A New Adrenergic Blocking Agent, J. Pharmacol. & Exper. Therap. **100**:119, 1950.

179. Lynn, R. B.: Effect of Priscol on Peripheral Circulation, Lancet **2**:678, 1950. Caufman, J.; Iglauer, A., and Herwitz, G. K.: Effect of Priscoline on Circulation and Skin Temperature in Normal Man, Angiology **1**:515, 1950. Jaensch, P. A., and Budde, H.: Priscoline for Retinal and Optic Nerve Disease, Klin. Monatsbl. Augenh. **116**:267, 1950.

180. Finnery, F. A., Jr., and Freis, E. D.: Experimental and Clinical Evaluation in Man of Hexamethonium (C6, New Ganglionic Blocking Agent), Circulation **2**:828, 1950.

181. Alve, L. H.: Double Effect of Dibenamine,® Med. Klin. **45**:1534, 1950.

effect; apparently, in small doses it facilitates adrenergic nerve impulses of the sympathetic nerve system, and in larger doses blocks them. Some of these effects cannot be explained on the basis of purely peripheral blocking mechanisms, and it may be that the central action of the drug must be considered.

PARASYMPATHOMIMETIC BLOCKING AGENTS

New agents capable of blocking cholinergic transmission have been introduced in recent years. "Banthine" is a quaternary amine. Its descriptive formula is β-diethylaminoethylxanthene-9-carboxylate methobromide. It has two principal types of action: an anticholinergic and an autonomic-ganglion-blocking action.

Compound 75GT was introduced into ophthalmology by Priestley and Medine.[182] It is a spasmolytic agent belonging to the class of basic esters and substituted phenylacetic acids. It may be used as a 0.5% solution in a boric acid-borate buffer, of approximately pH 5.7, with 1:50,000 solution of benzalkonium chloride added as a preservation. No irritation or untoward general reactions were observed after local instillation into the eye. It has both mydriatic and cycloplegic properties. As a cycloplegic, it is more effective than homatropine and less persistent. Another drug belonging to this group is bentyl, which also has an anticholinergic property.[183]

E-3, or lachesine, is slightly superior to homatropine as a mydriatic, according to Feldman.[184]

GANGLION-BLOCKING AGENTS

Because of structural relationship to acetylcholine, many quaternary ammonium compounds are pharmacologically active at cholinergic synapses and neuroeffector junctions. Any new compound in this group may be expected to have one or more of the following reactions: stimulation of cholinergic effector cells, stimulation of ganglion cells, stimulation of striate muscle, inhibition of transmission at these sites, and inhibition of cholinesterase. Quaternary ammonium compounds acting by each of these mechanisms have been described.[185]

Decamethonium (DCM) has been found to possess acetylcholine-like action at the neuromuscular junctions. The stimulatory action does not depend on its weak anticholinesterase activity. Both physostigmine and neostigmine, in doses ineffective by themselves, potentiate the stimulatory action of decamethonium. Denervated muscle acts similarly to decamethonium and acetylcholine. Since decamethonium resembles acetylcholine, its blocking action resembles depolarization on the motor

182. Priestley, B. S., and Medine, N. N.: A New Mydriatic and Cycloplegic Drug, Am. J. Ophth. **34**:572, 1951.

183. Hufford, A. R.: New Antispasmodic, Bentyl Hydrochloride, J. Michigan M. Soc. **49**:1308, 1950.

184. Feldman, J. B.: E-3 (Lachesine), Am. J. Ophth. **34**:442, 1951.

185. (*a*) Neuromuscular Blocking by Drugs, Editorial, J. A. M. A. **145**:322 (Feb. 3) 1951. (*b*) Paton, W. D. N., and Zaimis, E. J.: Actions and Clinical Assessment of Drugs Which Produce a Neuromuscular Block, Lancet **2**:568, 1950. (*c*) Grob, B., and Harvey, A. M.: Observations on Effects of Autonomic Blocking Agent, C5, in Normal Subjects and in Patients with Peripheral Vascular Disease and Hypertension, in Comparison with Tetraethylammonium Chloride, Bull. Johns Hopkins Hosp. **87**:616, 1950. (*d*) Arkin, H.; Sherman, I. C., and Weinburg, S. L.: Tetraethylammonium Chloride in Treatment of Multiple Sclerosis, Arch. Neurol. & Psychiat. **64**:536 (Oct.) 1950.

end plate. The main difference between decamethonium and *d*-tubocurarine is that *d*-tubocurarine paralyzes neuromuscular conduction by rendering the end plate less sensitive to the depolarizing action of acetylcholine. Decamethonium, like acetylcholine, depolarizes the end plate region and may, like acetylcholine, according to the circumstances, initiate a propagated contraction or give rise to neuromuscular block. Decamethonium should thus be compared to acetylcholine, rather than to curarine, in its action.[186]

The ocular effects of tetraethylammonium chloride can be explained by the ability of the substance to block the parasympathetic and sympathetic ganglion. Studies with pentamethonium iodide and related compounds, and with S. C. 1950, or 2,6-dimethyldiethylpiperidinum bromide, revealed similar ocular effects. These agents, when administered intravenously, block the local actions of anticholinesterase drugs, such as diisopropyl fluorophosphate and physostigmine, but not those of cholinergic drugs, such as carbachol U. S. P. They produce various degrees of mydriasis and relaxation of ciliary muscle, and also of lowering of the intraocular pressure.[187]

Curarine and curare-like agents are being used with increasing frequency for muscle relaxation in ophthalmic surgical anesthesia.[188] Drucker, Sadov, and Unna[189] compared the ocular effects of curarine and curarine-like drugs—*d*-tubocurarine, dimethyl-*d*-tubocurarine, and C10. C10 is decamethylene-1,10-bis-(trimethyl ammonium bromide). *D*-tubocurarine was the least potent but had the longest duration of action. C10 was the most potent but had the shortest duration. All these drugs produce questionable recession of the near points of monocular accommodation, without alteration of the visual acuity or of color perception. They produced weakness of the extraocular muscles, diplopia, and ptosis of varying degrees. In their experience, there was no change in intraocular pressure, although there was almost complete paralysis of the extraocular muscles.

Instillation of atropine into normal rabbit eyes did not affect the quantity of ascorbic acid, either reduced or in the oxidized form. A warning to avoid the use of atropine-like drugs before and after operation, as a possible responsible factor in the producing of hyphema, at least in respect to ascorbic-acid-reducing effects, seems unwarranted.[190]

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186. Editorial.[186a] Zaimis, E. J.: The Action of Decamethonium on Normal and Denervated Mammalian Muscle, J. Physiol. **112**:176, 1951. Paton, W. B., and Zaimis, E. J.: Action of D-Tubocurarine and of Decamethonium on Respiratory and Other Muscles in the Cat, ibid. **112**:311, 1951.

187. Drucker, A. P.; Sadove, N. E., and Unna, K. R.: Ocular Manifestations of Intravenous Tetraethyl Ammonium Chloride in Man, Am. J. Ophth. **33**:1564, 1950. Heyman, C., and Horrens, A.: The Effect of Tetraethylammonium on Miotic Action of Diisopropylfluorophosphate, Acetylcholine, Physostigmine, and Pilocarpine, Arch. internat. pharmacodyn. **83**:47, 1949. Reedy, W. J.: Comparative Effects of Ether, Alcohol, TEA and Priscoline in Producing Vasodilatation in Peripheral Vascular Conditions, J. Lab. & Clin. Med. **37**:365, 1951.

188. Cordes, F. C., and Mullen, A. R. S.: The Use of Curarine in Cataract Surgery, Am. J. Ophth. **34**:557, 1951. Farquaharson, H.: Curare with Local Anesthesia in Cataract Surgery, ibid. **34**:554, 1951. Jacobs, C.: The Use of Curarine and Pentothal® in Ophthalmic Surgery, read before the Third Clinical Conference of the Wills Hospital, March 16-17, 1951.

189. Drucker, A. B.; Sadov, N. S., and Unna, J. R.: Ophthalmic Studies of Curarine and Curarine-Like Drugs in Man, Am. J. Ophth. **34**:543, 1951.

190. Cassady, J. B.; Thompson, J. N., and Lon Pope, J.: Influence of Certain Mydriatics on the Ascorbic Acid Content of the Aqueous Humor, Arch. Ophth. **43**:813 (May) 1950.

There is some evidence that pilocarpine may have an enhancing action on sympathetic ganglion. There is also evidence that this effect is not blocked by tetraethylammonium chloride.[191]

Jaffe [192] demonstrated that localization of lesions causing Horner's syndrome may be accomplished by two methods: First, tests with cocaine, epinephrine, homatropine, and atropine, which help to determine the level at which the sympathetic chain has been interrupted, and, second, evaluation of signs and symptoms attributed to involvement of neighboring structures. Jaffe suggests the following combinations as pharmacologically significant in localization: (1) no reaction to cocaine, a strong epinephrine reaction indicating a lesion of the third neuron, that is, a postganglionic lesion between the superior cervical ganglion and the iris dilator fibers; (2) no reaction to cocaine, mild epinephrine reactions indicating a lesion of the second neuron, that is, between the ciliospinal center of Budge and the superior cervical ganglion; (3) a good reaction to cocaine, suggesting a lesion of the first neuron, between the hypothalamic area and the ciliospinal center of Budge.

In a true Horner syndrome, homatropine will dilate the pupil poorly. This test gives the same results no matter which neuron is interrupted.

PROCAINE AND COCAINE

Scheie and Ojers [193] produced evidence that procaine caused mydriasis in dog and cat eyes when directly injected into the anterior chamber. Pilocarpine and physostigmine were unable to overcome this mydriasis. This action was probably a direct effect of procaine, depressing the sphincter muscle cells. The authors suggest caution during intraocular surgical procedures in avoiding the possibility of procaine coming into contact with the iris, as such contact may lead to undesired sphincteric depression and mydriasis.

Velhagen [194] describes curative effects of retrobulbar or subconjunctival administration of procaine in cases of recurrent corneal erosion, serpiginous ulcers, neuroparalytic keratitis, and herpes zoster.[195] Intravenous injection of procaine has been employed for various ocular diseases thought to be due to vasospasm, with some favorable reports. It theoretically helps by relieving arteriolar constriction and pain. Procaine can be toxic by virtue of hypersensitivity and effects on the central nervous system.[196]

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191. Root, M. A.: Action of Pilocarpine on Sympathetic Ganglion, J. Pharmacol. & Exper. Therap. **101**:125, 1951.

192. Jaffe, N. S.: Localization of Lesions Causing Horner's Syndrome, Arch. Ophth. **44**:710 (Nov.) 1950.

193. Scheie, H. G., and Ojers, G. W.: Effect of Procaine and Cocaine on Iris, Am. J. Ophth. **33**:1543, 1950.

194. Velhagen, K., Jr.: Clinical and Theoretical Aspects of Neuralpathology and Therapy of the Eye, von Graefes Arch. ophth. **150**:459, 1950.

195. (*a*) Velhagen.[194] (*b*) Grossman, E. E., and Holm, A. G.: Amblyopia Following Post-Thyroidectomy Hemorrhage Relieved with Stellate Ganglion Block and Intravenous Procaine, Am. J. Ophth. **33**:1099, 1950. (*c*) Grossman, E. E.; Hitz, J. B., and Roncke, G. J.: The Use of Intravenous Novocain in Ophthalmology, ibid. **33**:1515, 1950.

196. Grossman and others.[195c] Steinhaus, J. E., and Tatum, A. L.: Experimental Study of Procaine Intoxication and Its Treatment, J. Pharmacol. & Exper. Therap. **100**:351, 1950.

TISSUE THERAPY

A considerable number of reports have been made for further evaluation of tissue therapy in ocular disease.[197] Results on the whole are not favorable, although they are conflicting, and the real value of the method in specific indications is extremely difficult to evaluate. However, the considerable continued interest, mostly in Europe, in this form of therapy suggests that the approach may have some merit and cannot be ignored.

Workers at the Pasteur Institute have prepared a serum of antireticuloendothelial cytotoxic material, which is known as orthobiotic serum. These investigators give the preparation of the extract in detail. Some benefits are reported, of temporary nature, in relieving glaucoma, retinitis pigmentosa, and interstitial keratitis; in healing eczema of the lids; in reducing scar formation of marginal ulcers of the cornea, and in increasing the accommodative power in presbyopia.[198]

Injections of vitreous extracts have been made with reported benefit in scarred areas of the orbit.[199]

MISCELLANEOUS TOXICOLOGY

Beryllium granulomas of the skin develop after wounds produced by broken fluorescent bulbs. The ophthalmologist, as well as other physicians, must be familiar with these lesions, because they are remediable if complete excision is achieved. The intravenous administration of certain beryllium-containing powders leads to development of osteogenic sarcoma. The only well-defined biochemical action of beryllium that is known is its inhibition of alkaline phosphatase in vitro.[200]

Yellow phosphorus is a powerful protoplasmic poison capable of producing serious pathologic alterations in almost all the organs of the body, more especially in the liver, heart, kidney, spleen, and brain. At present the commonest form of

197. Saldago Benavides, E.: Contribution to Tissue Therapy, Arch. Soc. oftal. hispano-am. **10**:890, 1950. Coppez, L.: Tissue Therapy in Ophthalmology, Bull. Acad. roy. méd. Belgique **15**:256, 1950. Marin Amat, N., and del Rio Cabanas, J. L.: Therapeutic Value of Implantations of Placenta, Arch. Soc. oftal. hispano-am. **10**:976, 1950. Guelbenzu, M. D.: My Experiences of Filatov's Tissue Therapy, ibid. **10**:983, 1950. Etzine, S.: Placental Implants in Ophthalmology, South African M. J. **24**:681, 1950. Raab, C.: Probable Mechanism of Tissue Therapy, Szemészet ophth. **87**:177, 1950. Schirru, M.: Placental Therapy in Ophthalmology, Ann. Med. **55**:69, 1950. Pollet-DeLille, and Pollet, J.: Two Cases of Sjögren's Syndrome: Favorable Action of Tissue Therapy, Bull. Soc. opht. France, p. 138, 1950. Collier, M.: Tissue Therapy in Severe Herpetic Keratitis, ibid., p. 149, 1950. Vianna, L.: Tissue Therapy, Rev. brasil. oftal. **8**:211, 1950. Tschentsov, A. G.: Further Observations in the Use of Tissue Therapy in Ocular Disease, Vestnik oftal, **29**:42, 1950. Barrois, P.: Recent Results of Russian Research with Tissue Therapy, Ann. ocul. **183**:957, 1950. Panepinto, V., and La Cascio, G.: Treatment of Retinitis Pigmentosa According to Filatov's Method, Gior. ital. oftal. **3**:311, 1950. Kozlowski, B.: Results of Treatment of Retinitis Pigmentosa by Placental Implantation, Polski. hyg. lek. **5**:538, 1950. Perez Torel, F.: On Filatov's Therapy, Arch. Soc. hispano-am. **10**:74, 1950. Tschentov, A. G.: Long-Term Observation on Use of Tissue Therapy in Ocular Diseases, Vestnik oftal. **29**:42, 1950.

198. Bourdier, F., and Golovine, S.: Trials in Ocular Therapy Using the Orthobiotic Serum of Pasteur Institute, Bull. Soc. opht. France, p. 30, 1950. Galovine, S.: The Treatment of Ocular Infections with "Orthobiotic" Serum of the Pasteur Institute, Presse méd. **58**:393, 1950.

199. Sverdlov, E. G.: Treatment of Scars by Injection of Vitreous Extract, Vestnik oftal. **29**:24, 1950.

200. Large, H. L., Jr., and Stumpe, A. R.: Cutaneous Beryllium Granuloma, South. M. J. **44**:36, 1951. Hoagland, M. B.; Frier, R. S., and Hood, M. B.: Beryllium and Growth, Cancer Res. **10**:629, 1950.

acute poisoning is from ingestion of the element contained in rodent exterminators, either accidentally or with suicidal intent. The only ocular sign which is mentioned in the various reports is jaundice.[201] Although various insecticides can produce ocular changes by virtue of anticholinesterase activity, there are some which in the usual exposure concentrations do not produce any ocular effects, such as chlordan, aldrin, and dieldrin.[202] Propylene glycol dipropionate and other compounds investigated for use as inhibitors of biologic processes were found to have no significant irritant effect on mucous membrane of the eye.[203]

Various aliphatic amines that are used in the manufacture of softening agents, as flame retarders for certain paper products, and as accelerators in the synthetic rubber industry, were shown to produce ocular damage, such as multiple punctate erosions and edema of the cornea. There is a latent period before signs develop.[204]

Because of the close association of vitamins A and D to ophthalmology, attention is called to references made in the literature relating to the toxicity of excess vitamin A and D.[205]

Picrotoxin is a stimulus of the nervous centers of the cortex of the brain stem that produces no alteration of ocular tension, ocular motility, or the fundus. It would appear to have no harmful effects on the eye.[206]

Repeated paracentesis of the rabbit cornea, beginning one-half to 45 min. after exposure to ammonia, resulted in no significant improvement at any time over the condition in 17 control eyes. It is concluded that the treatment of chemical burns of the eye by repeated paracenteses is not favored by experimental evidence at present available.[207]

Smith [208] describes an eye from which he removed a cilium and discusses the possibilities of what may happen when the cilium is left in the anterior chamber. Pereyra [209] also mentioned the development of iridocyclitis after retention of a cilium in the anterior chamber for three months. Ferrel [210] observed an eye with a piece of suture in the anterior chamber after cataract operation that was well tolerated.

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201. Dias Rivera, R. S.; Collazo, P. J.; Pons, E. R., and Torres Grosa, N. B.: Acute Phosphorus Poisoning in Man, Medicine **29**:261, 1950.

202. Prince, S., and Spurbeck, G. H.: A Study of Workers Exposed to the Insecticides, Chlordan, Aldrin, and Dieldrin, A. M. A. Arch. Ind. Hyg. & Occ. Med. **3**:64 (Jan.) 1951.

203. Ambrose, A. M.: Toxicologic Studies of Compounds Investigated for Use as Inhibitors of Biologic Processes: III., ibid. **3**:48 (Jan.) 1951; IV., ibid. **3**:52 (Jan.) 1951.

204. Brieger, H., and Hodes, W. A.: Toxic Effects of Exposure to Vapors of Aliphate Amines, ibid. **3**:287 (March) 1951.

205. Caffe, J.: Chronic Poisoning Due to Excess of Vitamin A, Am. J. Roentgenol. **65**:1219, 1951. Fried, C. T., and Grand, A. J. H.: Hypervitaminosis A, Am. J. Dis. Child. **79**:475 (March) 1950. Christensen, W. R.; Liebman, C., and Sosman, N. C.: Skeletal and Periarticular Manifestations of Hypervitaminosis D, Am. J. Roentgenol. **65**:27, 1951.

206. Esente, I.: Ocular Findings Following Use of Picrotoxin, Gior. ital. oftal. **3**:433, 1950.

207. Grant, W. M.: Experimental Investigation of Paracentesis in the Treatment of Ocular Ammonia Burns, Arch. ophth. **44**:399 (Sept.) 1950.

208. Smith, J. W.: Cilium in the Anterior Chamber, Arch. ophth. **44**:424 (Sept.) 1950.

209. Pereyra, L.: A Case of Penetrating Eyelashes in the Anterior Chamber and Lens, Gior. ital. oftal. **3**:286, 1950.

210. Ferrel, J.: Suture Material in the Anterior Chamber After Operation for Cataract, Algérie méd. **54**:47, 1950.

It was observed [211] that three of every four operative wounds were contaminated with foreign matter, which might have been cotton fibers, talc, or rubber, without undue reaction.

Emetine will produce conjunctivitis, corneal opacification, and ulceration. Lasky [212] suggests denudation of the corneal epithelium as a therapeutic measure for reducing the severity of the resultant lesion.

Acetone will produce corneal clouding.[213]

Ocular findings from exposure to carbon disulfide include optic neuritis in 10% of the cases. Contraction of the field of vision with central scotoma, paresis of pupillary reflexes, and involvement of the extraocular muscles have also been reported.[214]

Since the war, fluorine compounds have found wide industrial use in products such as dyes and plastics, pharmaceuticals, tanning agents, metal, fluxes, fumigants and insecticides, fungicides, germicides, fire extinguishers, solvents, fireproofing compounds, and heat-transfer mediums. The acids and their more soluble salts cause necrosis and ulceration, and the subsequent sloughing and slowly healing yellow ulcers, when they come in contact with the skin. Ocular effects include ulceration of the conjunctiva, light sensitivity, and continuous conjunctival secretion. These local effects are best treated by copious lavage and ointments containing metallic oxides, such as magnesium oxide, which combines with fluorides.[215]

A piece of glass was embedded in an intraocular structure in the iris for approximately 45 yr. without causing deterioration of vision or changes in the fundus. Cohen points out that 98% of the glass is made up of neutral sodium silicate, which is chemically inert.[216]

Trimethadione and "paradione" are anticonvulsant drugs used in the treatment of petit mal. They appear to interfere with retinal metabolism.[217] Dimedione (3,5-dimethyl-5-ethyloxazolidine-2,4-dione) is a new antiepileptic drug for the treatment of petit mal in children. No toxic damage could be demonstrated to the nervous elements in rabbits given 100 to 200 mg. of dimedione daily for two to 20 wk.[218]

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211. Duscynski, L. L.: The Contamination of Operative Wounds with Cotton Fiber and Towel, Tr. Am. Acad. Ophth. 1950, p. 110.

212. Lasky, M. A.: Corneal Response to Emetine Hydrochloride, Arch. Ophth. **44**:47 (July) 1950.

213. Gomer, J.: Turbidity of the Cornea Caused by Pure Acetone, von Graefes Arch. Ophth. **150**:622, 1950.

214. van Leeuwen, M. A., and André, M. J.: Probable Case of Diplopia Due to Carbon Bisulfide, Rev. oto.-neuro.-ophthal. **22**:509, 1950. Roger, H., and Roger, J.: Neurological Features of Carbon Disulfide Poisoning, Ann. M. Psychol. **1**:1, 1950. Masure, R.: Keratitis and Viscose Factories, Arch. belges méd. Sociale hyg. **7**:509, 1950.

215. Larner, J.: Toxicological and Metabolic Effects of Fluorine-Containing Compounds, Indust. Med. **19**:535, 1950.

216. Cohen, M.: Iris Cyst Following Traumatic Implantation of Glass Splinter, with Foreign Body Probably Retained in Ciliary Area 45 Years, A. M. A. Arch. Ophth. **45**:413 (April) 1951.

217. Gilger, A. D.; Potts, A. M., and Johnson, L. D.: Effect of Anticonvulsant Drugs on Retinal Metabolism, Ohio M. J. **46**:883, 1950.

218. Christensen, S.; Engelbrecht-Holm, J., and Anderson, S. R.: Toxic Effects of Dimedione (Didione) on the Eye and Visual Nerve Path of Rabbits, Nord. med. **43**:875, 1950.

Retrobulbar neuritis has been reported after trichloroethylene[219] and optic atrophy after sodium cacodylate injections,[220] and Aspidium filix-mas.[221]

219. Palich-Zanto, O.: Significance of Trichloroethylene in the Causation of Retrobulbar Neuritis, Nepegeszsegugy, Budapest, **31**:637, 1950.

220. de Troy, U., and Lesenne, E.: Bilateral Optic Atrophy Following Injections of Sodium Cacodylate in a Woman Suffering from Scleroderma, Bull. Soc. opht. France, p. 135, 1950.

221. Borovy, A. V.: Atrophy of the Optic Nerve Following Intoxication by Aspidium Filix-mas, Česklov. oftal. **6**:301, 1950.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

R. Townley Paton, M.D., *Chairman*

Raymond L. Pfeiffer, M.D., *Secretary*

Regular Meeting, Jan. 15, 1951

CLINICAL PRESENTATIONS

Ocular Mucormycosis. Dr. Joseph A. C. Wadsworth.

A case of ocular mucormycosis was presented. The fungous infection apparently affected the retina and choroid so as to resemble retinitis exudativa (Coats's disease). Microscopic examination revealed the organisms in the tissue. Recovery of the organism by numerous cultures and examinations was never possible. A short review of the literature was given. In all the previously reported cases the patients had diabetes and died. In this case the patient was a healthy young man without diabetes. This is the only case known in which the eye alone was involved.

Present Day Problems in Mycology. Dr. J. Gardner Hopkins.†

The Diagnosis of Ocular Mycotic Infection. Dr. Henry L. Birge (by invitation).

Fungous diseases present a major problem in diagnosis, as well as treatment, and should be considered in the differential diagnosis of all infectious diseases that concern the ophthalmologist.

The rarity of fungous infections of the eye and the voluminous literature combine to make the true picture of ocular mycotic infection more obscure than in reality it is. Pathogenic fungi form but a small percentage of the fungi that inhabit the surface of the earth, the soil, the air, the animals and the plants of this planet. When routine fungous cultures of the eye are taken, it is easily possible to isolate over 42 species. Only 14 species of fungi are known to be pathogenic to man. Fungi may be separated into (*a*) contaminants, or saprophytes, and (*b*) pathogenic fungi. The contaminating fungi which most frequently confuse the clinician are those which grow in such cultural abundance that they appear to be the etiologic agent, or a secondary invader; these are (1) Aspergillus (except Aspergillus fumigatus), (2) Mucor and (3) Penicillium. Mycologists are reluctant to ascribe any pathogenicity to these common contaminants.

The diagnosis of ocular mycotic infection depends primarily on keeping the possibility in mind and on a good mycologist. Fungous cultures require special handling by an expert. Identification of the organisms may be made in a few hours or may take weeks, as in the case of Histoplasma capsulatum. A few fungi have still to be cultured. Animal inoculation often saves time in making the diagnosis; yet in some cases the lesions found in man cannot be reproduced in animals. Immunization reactions to the fungi, both as pathogenic and as therapeutic agents in the form of antibiotics, are well known. They are used as aids in diagnosis, especially with monilial infections, in which the hypersensitivity of the patient supports the evidence that the organism isolated is in reality that causing the disease.

A valuable point to remember about mold allergens is that patients may show allergies to more species than the 14 pathogenic fungi. This is especially true of asthmatic patients, who may suffer from allergy to nonpathogenic molds. Cutaneous immunization reactions are valuable diagnostic aids in both coccidioidomycosis and sporotrichosis. They are less valuable in blastomycosis and histoplasmosis. Agglutination tests may be called for in the diagnosis of North American blastomycosis, moniliasis and coccidioidomycosis.

† Dr. Hopkins died on February 27, before he could prepare the paper for publication.

Roentgenography will aid the ophthalmologist in making the diagnosis of systemic disease, especially if he will bear in mind that some of the calcified pulmonary plaques formerly considered tuberculous may have been mycotic. Smears of blood may show the intracellular parasite in histoplasmosis or cryptococcosis. Lumbar puncture, with examination of the centrifuged specimen or culture, may prove the presence of cryptococcosis. Fluid from cysts of the retina should be examined for the Cryptococcus.

Almost all mycotic infections of the eye have their initial lesion in or near the eye, primarily by metastasis or through the unknown morbid processes of the disease, as in histoplasmosis.

It is important to note that most fungi invade man only after some sort of trauma, and often such mild trauma as to be unnoticed except when the cornea is injured. Another feature of fungous infection in man is its unpredictability. Inoculation with supposedly virulent strain does not always lead to infection, as will be shown later. On the other hand, several fatalities have occurred in laboratory workers, and caution in handling pathogenic fungous cultures is imperative.

The importance of ocular infection by pathogenic molds has perhaps been underestimated. The number and variety of ocular fungous diseases become impressive, ranging from lacrimal plugs, conjunctivitis and blepharitis to corneal ulcer, exophthalmos, detached retina and involvement of the central nervous system.

Any of the pathogenic molds may cause local ocular involvement. The fatalities occur only in the case of the molds that produce deep systemic involvement. The systemic lesions are in most cases similar to tuberculosis, carcinoma or syphilis, with the formation of abscesses and giant cells.

DISCUSSION

Dr. Frederick H. Theodore: All of us have been rewarded by having the opportunity to listen to such authorities as Dr. Hopkins and Dr. Birge on an extremely timely topic, fungous infections. I have little to add. Perhaps several points, though not very important, may be valuable clinically.

Dr. Hopkins mentioned the increasing importance of monilial infection, now that aureomycin, chloramphenicol and terramycin are used so much. He did not mention that there have already been several fatalities from monilial infection of the lung. Another important, and frequently encountered, condition which may be related to mycology is penicillin sensitivity. A number of dermatologists believe that penicillin sensitivity is actually a dermatophytid, and there is considerable evidence for this opinion.

In discussing Dr. Birge's paper, I should like to emphasize that, fortunately for us as ophthalmologists, there are only a few important fungi which we encounter in office practice, among them the Pityrosporum ovale, which Dr. Hopkins believes is not a pathogen but is associated with seborrheic blepharitis, and the Streptothrix, which is found in the lacrimal canaliculi. Dr. Hopkins made the point, which is only too true, that we usually do not employ specific mediums for fungi, even in institutions where cultures of the conjunctiva and lids are routine. Fortunately, in the two infections I mentioned epithelial scrapings are sufficient for identification of the fungus, and clinical examination often leads to the correct diagnosis without any laboratory aids.

I shall show slides illustrating several clinical cases.

(Slide) Blastomycosis. As you noted from Dr. Birge's map, there is an endemic area around Chicago, and this picture came to me through the courtesy of Dr. H. Saul Sugar. I believe it was taken when he was in Chicago.

(Slide) An infection of the cornea with Aspergillus. As Dr. Birge mentioned, Aspergillus is usually a benign organism, but this variety of Aspergillus fumigatus, when it attacks the cornea, causes a severe infection. The infection usually follows

injury by a foreign body. One must curet the lesion and cauterize it; thus, a serious corneal opacity results. Dr. Sugar supplied the original copy of this picture.

Parinaud's oculoglandular syndrome has always fascinated me, and apparently many other ophthalmologists. They always ask about it on the American Board examinations and want to know the cause of the condition. It has a number of causes, but I think the most important is a fungous infection.

(Slide) Leptotrichosis conjunctivae, the major cause of Parinaud's oculoglandular syndrome. (Dr. Alson E. Braley furnished the picture.) The diagnosis can be made only by biopsy, using the special Verhoeff stain.

(Slide) Parinaud's oculoglandular syndrome. The patient, an Army officer, had an infection of the upper lid with granulomatous lesions and enlargement of a preauricular gland, which ended in suppuration.

(Slide) Lesion, from another case, which looks very similar to the one just shown. It was gray and granulomatous and eventually cleared up. Biopsy seemed to help therapeutically in this case, as in many other cases reported. This slide is a section of the biopsy specimen. A budding yeast was found, and even though we warned the laboratory technicians to expect a yeast, culture of the gland was thrown out because they said it was contaminated.

I do not think that streptotrichal infections of the canaliculus are rare. I myself, in a relatively short period of observing this condition, have encountered about 30 cases. I think that the term Streptothrix, although misleading, is a good one to reserve in ophthalmology. The organism is a low grade type of actinomyces, but if we refer to the condition as actinomycosis we confuse the issue.

(Slide) Swellings like the one here are often taken for a chalazion; but when one can express pus from the dilated canaliculus, one may be sure that the condition is due to the Streptothrix. If one obtains concretions, one can be almost positive, although Aspergillus may give the same picture. An interesting thing about streptotrichal infections is that they seem to occur only in canaliculi which have diverticula. This must be borne in mind for the successful eradication of these molds. The best procedure is to curet the entire canaliculus, using procaine infiltration, and then inject a small amount of 1 per cent iodine. Sometimes, as you know, the upper canaliculus is the only part involved; often both canaliculi are infected.

(Slide) A stained crushed concretion from such a canaliculus. The fungus is a branched, typical Actinomyces, while the Leptothrix is not branched. The peculiar filamentous organisms here are hard to mistake for anything else.

Sometimes, however, in streptotrichal infections there is no obvious involvement of the canaliculus. (Slide) This picture is one from such a case, with severe unilateral conjunctivitis for six months. There was so much discharge that the patient had to wash his eye out every 15 minutes. The diagnosis had not been made, although suspected, because irrigation of the lacrimal passages had been done successfully. However, in Streptothrix infection there is generally little obstruction of the lacrimal passages. When an epithelial scraping was made, I saw the fragmented or coccoid bodies that are present when the mycelia are broken up, and the diagnosis was immediately suspected. In other words, when, on examination of a scraping, one sees these little coccoid organisms, which look too small for Streptococcus or Staphylococcus, one must always think of Streptothrix. In a few cases reported this was the only way in which diagnosis was possible. In this particular case, when I saw the smear showing the suspicious organisms I examined the lacrimal passages, although they appeared normal. I always feel apologetic for bringing up the subject of Streptothrix infection, for the condition is so common; often, however, only one case will be reported at a clinical meeting.

The last subject I wish to discuss, the yeast Pityrosporum ovale, is one on which Dr. Hopkins has spoken at considerable length. He believes that it is a harmless

saprophyte. Dr. Thygeson, however, feels definitely that it is a pathogen and that it causes the seborrheic type of blepharitis. Most dermatologists believe it is a saprophyte and of no pathologic significance. Both opinions may be correct. Apparently, in persons with a seborrheic diathesis something happens to the normal fatty acids of the skin; they change in quantity and amount, and the organisms that are ordinarily saprophytic, such as Pityrosporum and staphylococci, may become pathogens. Even if we assume that Dr. Hopkins is correct, and that the organism is not a pathogen, we can at least, by making scrapings and finding large numbers of these organisms, make a diagnosis of seborrheic blepharitis, rather then staphylococcic blepharitis, and treat the infection accordingly. The ordinary antibiotics have no effect on the seborrheic type of blepharitis. Even if this yeast is not the cause of the disease, it is a means of making the diagnosis.

(Slide) A mixed type of blepharitis, in which both a toxic Staphylococcus and the yeast were found. Note the greasy, easily removed scales of seborrheic blepharitis. When these scales are removed, ulcers are not found as in the staphylococcic type; only a red skin is seen beneath.

(Slide) A drawing of the yeast Pityrosporum ovale, showing budding.

(Slide) Photomicrograph of a scraping from the lid margin also showing the budding yeast. The patient was a peculiar person. In addition to the blepharitis, she had a large amount of dandruff, but she refused to treat it. The only thing she would accept for her lids were free samples of sodium propionate ointment. This kept her lids completely clear as long as she used the drug. I feel that in this case, a deficiency existed as part of the seborrheic diathesis.

(Slide) Cultures of Pityrosporum ovale on wort agar. Good growth after 14 days' incubation is seen on the first plate. No growth occurred in the plate to which 5 per cent sodium propionate was added.

I have been asked by Dr. Birge to mention the fatty acid therapy of fungous diseases. My personal experience is somewhat limited, but good results have been reported with the use of sodium propionate in infections with Trichophyton, Epidermophyton, Microsporum, Candida, Torula, Coccidioides, Aspergillus, Blastomyces and Actinomyces. A recent article (Crook, P.; Carpenter, C. C., and Klens, P. F.: Use of Sodium Propionate in Isolating Actinomycetes from Soils, *Science* **112**: 656 [Dec. 1] 1950) reported the use of sodium propionate in 0.4 per cent solution, in special agar, in order to grow Actinomyces, because it eliminates the secondary contaminants. However, with an 0.8 per cent solution of sodium propionate in the medium, no growth occurred.

R. Townley Paton, M.D., *Chairman*

Raymond L. Pfeiffer, M.D., *Secretary*

Regular Meeting, Feb. 19, 1951

CLINICAL PRESENTATIONS

Retinoblastoma Treated by Diathermy. DR. CHARLES A. PERERA.

Bilateral retinoblastoma requires enucleation of the more involved eyeball together with a segment of the orbital portion of the optic nerve. If the less affected globe has useful vision and the tumor is behind the equator, it can be treated by roentgen radiation. If the growth in the second eye lies anteriorly, it may be destroyed by diathermic coagulation in selected cases. The literature dealing with this method was reviewed, and the case of a white boy aged 7 years was reported. His inflamed right eye contained retinoblastoma, with complete detachment of the retina. The left eye harbored a peripheral tumor of the retina in the superior nasal quadrant. Enucleation of the right eyeball was performed, followed by diathermic

coagulation of the lesion of the left eye. Healing was uneventful, with normal vision in the left eye and no evidence of recurrence at the time of report, 2¼ years after operation. Pathologic study of the removed globe showed retinoblastoma.

Primary Carcinoma of the Nasolacrimal Sac. DR. JOHN C. LOCKE (by invitation).

As pointed out by Spratt, the course of primary carcinoma of the nasolacrimal sac may conveniently be divided into three stages. In the first stage, epiphora is the only sign, and correct diagnosis is difficult or impossible. The second stage is that of swelling, and here differentiation lies chiefly between tumor and mucocele. In the third stage, there are ulceration, metastasis to the neighboring lymph nodes and spread to the nasal mucosa, lids or orbit, and the diagnosis presents little difficulty.

In the case of mucocele, the nasolacrimal duct is generally obstructed, while in tumor it may be patent. Pressure on a mucocele will usually cause return of fluid from the punctum or into the nose, with diminution in the size of the swelling, while pressure on a tumor does not. Finally, the roentgenogram following the injection of iodized oil U. S. P. into the nasolacrimal system gives valuable aid in diagnosis.

A white man aged 45 was first seen in September 1948, complaining of tearing of the right eye. Except for mild epiphora on the right side, examination of the eyes revealed nothing abnormal. On irrigation of the sac, the solution passed freely into the nose. The tearing was relieved, only to return in three weeks.

Further irrigation brought about the same sequence of events, i. e., temporary relief from tearing, followed later by its recurrence.

In May 1950 a swelling was noted in the region of the right nasolacrimal sac. The swelling would not collapse on pressure, nor could pus or other fluid be expressed. The nasolacrimal system could still be irrigated.

Roentgenograms taken after the injection of iodized oil into the right nasolacrimal system showed a large lobulated shadow in the position of the sac, which in the lateral roentgenograms was curved forward in such a manner as to suggest a mass, posterior to and encroaching on this structure. A large collection of oil present in the nasal fossa indicated the patency of the lacrimal system.

At operation, the sac was found to be filled with a lobulated, gelatinous, avascular mass. This was excised, and an attempt was made to remove as much as possible of the upper canaliculus and all suspicious tissues surrounding the sac.

The pathologic diagnosis was epithelioma of the nasolacrimal sac, of the columnar cell type.

Most of the cases of carcinoma described in the literature have been of the invasive or infiltrative type. This case was apparently unique in being a carcinoma in situ, all of the epithelial proliferation having occurred on the lumen side of the basement membrane, with no penetration of the membrane detectable anywhere. Accordingly, if the tumor has been completely removed, it should not recur. At the time of the report, the patient had been followed for six months, with no recurrence.

A rare, and not previously reported, type of secondary carcinoma of the nasolacrimal sac, one originating in Bowen's intraepithelial epithelioma of the bulbar conjunctiva, was presented. Bowen's disease is a noninfiltrative type of carcinoma, with characteristic histopathologic features, which spread by lateral extension, rather than by invasion of deeper tissues. In this case the tumor had been present on the bulbar conjunctiva for five years, with no evidence of infiltration through the basement membrane. When it reached the nasolacrimal sac, however, it became malignant and took on the characteristics of a relatively dedifferentiated squamous cell carcinoma.

PAPERS OF THE EVENING

Optic Neuritis: A Fifteen Year Study. Dr. Frank D. Carroll.

During the past 15 years, the author studied 240 patients with optic neuritis and followed them over a long period. He excluded from consideration 145 patients with tobacco-alcohol amblyopia seen during the same period. Of patients with optic neuritis, 23 per cent complained of pain in the head, and 16 per cent had tenderness to palpation of the globe. This, with pain on movement of the involved eye, points to the diagnosis of optic neuropathy and away from a diagnosis of intracranial tumor.

Nine patients had disease of structures adjacent to the optic nerve, in the following distribution: orbital cellulitis, two; sinusitis, two; sinusitis (?), three; osteosclerosis of the skull, one; chronic tuberculous meningitis, one. Thirteen patients had infectious diseases, usually generalized, which caused the optic neuritis: syphilis, two; infection of the upper respiratory tract, three; influenza, three; mumps, one; vaccinia, one; focus of infection (?), two; encephalitis after mastoidectomy, one.

Noninfectious conditions produced optic neuropathy in 14 patients: pernicious anemia, two; loss of bood, two; nutritional anemia, three; trauma, one; metastatic carcinoma (breast), one; allergy, two; allergy (?), three.

Toxic agents were responsible in seven cases: methyl alcohol, two; thallium, one; spinal anesthesia, two; lead (?), two.

Nineteen patients had Leber's disease (hereditary optic atrophy). This occurred in 14 unrelated families. The possibility of a hereditary basis must be considered in every case of optic neuritis of obscure origin.

Vascular diseases accounted for the condition in 31 patients: arteriosclerosis, 14; hypertension, 8; arteritis (?), 5; unclassified, 3; rheumatic heart disease, 1. In early cases anticoagulants may be of value.

Multiple sclerosis produced optic neuritis in 46 patients; 24 others probably had multiple sclerosis, and 7 had neuromyelitis optica, a total of 32 per cent of the entire series. Sixty-four patients under the age of 50 admitted numbness in the extremities, whereas only seven over this age complained of it on questioning. A patient should never be told that he "may have multiple sclerosis." Years of worry and apprehension may result from such a statement.

Seven patients had severe bilateral optic neuritis with reduction of vision to nil or almost nil in both eyes. On conservative treatment five made a good recovery.

The etiology was undetermined in 30 per cent. There is no specific treatment for multiple sclerosis. The value of pituitary adrenocorticotropic hormone (ACTH) and cortisone in optic neuritis is being investigated. At present, in the cases of optic neuritis of unknown cause hormonal therapy seems of value in improving the general health and nutrition of the patient.

Movable Postenucleation Implants: Complications and Their Solution in a Series of over One Hundred and Twenty Implantations Performed During a Period of Thirty-Six Months; A Preliminary Report. Dr. William Stone Jr., Boston (by invitation).

DISCUSSION

Dr. Conrad Berens: I hesitated when I was asked to discuss Dr. Stone's paper, for only two such implantations have been performed in my service and I have so often seen unpleasant results follow placing of my own plastic integrated implants and those of other surgeons that I was afraid I might be biased against implants of this type. I accepted because, after seeing Dr. Stone's demonstration and obtaining a report on his operative and postoperative results, I believe that this type of work may offer a satisfactory solution of an important problem. Dr. Stone's results, so far, seem unusually good, and his meticulous care in operating and in after-treatment probably accounts for his excellent results, with no extrusions and no infections behind the implants.

My former associate, Dr. M. C. Loutfallah, was most enthusiastic about the Stone implant at first, but longer postoperative observation prompted the following telegram:

"Immediate results with Stone's implants unexcelled, but late results very disappointing. Discharge profuse in all cases. Often granulation tissue formation limiting motion and causing bleeding. Secondary infection required removal of implant with such conjunctival shrinkage that no other implant could be placed in deformed socket."

In a study of the files of the New York Eye and Ear Infirmary, Jacobson and I found that 20 integrated implants had been removed in the past five years.

Types	*No. of Implants*
Hughes	14
Berens	3
Stone-Jardon	2
Cutler	1
	20

In order to determine the trend in enucleation surgery at the New York Eye and Ear Infirmary, a study was made of the 81 enucleations and eviscerations performed during the last 11 months. (The statistics have been verified by Dr. F. A. Rosa.)

Enucleations		76
With gold ball implants, 12 to 18 mm. diameter	43	
With Trautman implants	15	
With Stone-Jardon implants (integrated)	1	
With Hughes vitallium® implant (integrated)	2	
Without implant	13	
Record not clear whether implant had been placed	2	
Evisceration		5
Evisceration implants of Rosa type	2	
No material implanted	3	

It may be seen from the work of the New York Eye and Ear Infirmary that many integrated implants have been removed and that the major trend is back to enucleation with gold ball implantation. Hughes (Hughes, W., in discussion on Stone, W.: Movable Postenucleation Implants, *J. A. M. A.* **145**:375 [Feb. 10] 1951) reported a study of 250 (90 Stone-Jardon) implants. One in 7 has been extruded spontaneously or has been removed because of orbital cellulitis or excessive discharge.

The experiences I have had, and those reported by others, had made me turn back to the buried plastic implants that were reported in 1941 (Berens, C., and Rothbard, S.: Synthetic Plastic Material for Implantation into Orbit Following Enucleation, *Am. J. Ophth.* **24**: 5, 1941). I now prefer the truncated cone type, hollowed for lightness, with a tantalum mesh collar for attachment of the rectus muscles, so that the implant will not migrate. I have also had considerable cosmetic success and no extrusions with plastic implants into the sclera.

Secretion has always been troublesome in many of our cases, and we have not always been so successful as Dr. Stone with antibiotics, even when the sensitivity of the organism to antibiotics has been determined. I believe his hygienic routine is probably responsible for the improved control of secretion, and this assumption is borne out by his report of his last 52 cases. Nothing is said of the relation of the infections of the socket to nasal infections. I believe that the nasal membranes are often the source of ocular inflammation (Berens, C., and Nilson, E. L.: Relationship Between the Bacteriology of the Conjunctiva and Nasal Mucosa, *Am. J.*

Ophth. **27:747, 1944**) in many cases and that this may also be true of coliform bacteria, which we found in 30 per cent of nasal cultures in serious ocular inflammations (Berens, C., and Nilson, E. L.: Ocular Conditions Associated with Coliform Bacteria, ARCH. OPHTH. **26:** 816 [Nov.] 1941).

Prevention of polyps and granulomas by greater care in suture of Tenon's capsule is encouraging. These complications must also be limited by his clever use of the small prongs instead of sutures for the muscles. The exposure of the meshwork is an unpleasant complication, which I saw in one of Dr. Loutfallah's cases. Dr. Stone insists on more space between the meshwork and the implant, and his efforts to obtain a more uniform mesh should aid materially in preventing this complication.

His results with delayed implants are phenomenal. However, from what Dr. Rosa tells me after his trip to Boston, unless we are willing to give up three or four hours to the operation, we should not do it ourselves, or our final results will probably be disappointing.

Several questions have occurred to me which I hope Dr. Stone will answer:

1. Would you consider it advisable to make the implants lighter?
2. The implants are very expensive. Is it possible to make them cheaper?
3. What is your experience with integrated implants into the sclera?
4. It would seem that the experience of other surgeons in reporting late results has been similar to Loutfallah's. If this is so, what should be done to obtain results comparable to yours?
5. So far, I have not seen an allergic reaction to the plastics (lucite or plexiglas®) I have used since 1941. Have you had any?

I hope that Dr. Stone will be able to continue his fine work, with adequate funds, for I am confident that he is making excellent progress toward a solution of this important problem. It is encouraging to see how cleverly he is planning to overcome the difficulties inherent in the distribution of a product that requires constant careful supervision by experts on a research basis.

DR. WILLIAM STONE, Boston: I should like to thank Dr. Berens for his discussion, and I shall try to answer some of his probing and interesting questions.

As to the price of the implant, about eight or nine months ago we started to make our own implants at the Massachusetts General Hospital. We used cast plastic of the annealed type, rather than injection-molded plastic, as has been used and is being used in most implants. We turned to the cast stock because the injection-molded stock is much softer than the cast stock and is porous, and thus absorbs much more fluid than does the cast stock. We have found that the labor of machining an implant, after the techniques are solved, takes approximately one hour. The labor of making the injection-molded implant takes approximately three to four minutes. The cost of tooling the injection molding is mainly the cost of the production of the die, which is $500 to $700, and of the injection molding machine, which is $800 to $900. The rest of the cost of the injection-molded implant is labor, and the labor cost of injection is small, whereas with the machine implant the labor is much greater, and it still takes approximately only an hour to make the implant. The cost of the machinist at the present rate is $1.65 to $1.85 an hour. The materials that go into the implant cost about $2.35. When we return the implant product to the manufacturers, therefore, we hope to be able to prevail on them, on the basis of the cost of the product, to make implants at a much reduced price.

As to scleral implants, I personally have had no experience with them. Dr. Cutler has found that scleral tissue does not grow into the meshwork very readily, and lately he has been in the habit of cutting small holes in the sclera to allow the surrounding connective tissue to grow into the meshwork. We have not used intrascleral implants, for the following reasons:

1. We think there are few cases in which they are indicated.
2. Very often we want to recess or resect a muscle, so that it does not make any difference whether the sclera is there or not.

3. The motility we get with the added bulges on the implant to serve as fulcrums is actually greater in the implant portion in the majority of cases than the motility of the original eyeball. If the motility is so good without the sclera, it does not seem reasonable to use it.

4. If intrascleral implants were used routinely, it would impede the science of ophthalmic pathology considerably.

With regard to antibiotics, we have found in clearing Esch. coli of late that chloramphenicol in a 25 per cent ointment and in 2 per cent drops in sorethytan (20) monooleate (Tween 80®) every two hours has been extremely effective. Penicillin has been used only as a prophylactic against gram-positive organisms. It has been very effective in cases of Staphylococcus aureus, much more effective than sulfacetimide, which we have also tried for Staph. aureus.

I am much interested in Dr. Berens' comment on Esch. coli in the nasal passages. In all the cases which have been shown, I hope to culture every nasal passage and see if I can corroborate Dr. Berens' results. The case of one boy who had his implant placed approximately 2½ to three years ago is interesting. Although he has no chronic secretion, each time that he has a severe head cold he has a discharge from the socket, and each time he has a discharge from the socket we culture Pneumococcus and Staph. aureus; so that there must be a definite relation between the activation of the organisms in the nose and the activation of any organisms in the socket.

As to the weight of the implant, I have had no experience with any implants sinking in a period of four years, and I do not know whether they will or not.

I have seen no cases of sensitization to the plastic. I have had none of the typical allergic manifestations in regard to implants, except when I have used several medications.

In reply to Dr. Berens' question as to whether the implant can be used by anyone else, I do not see why it cannot.

News and Comment

EDITED BY DR. W. L. BENEDICT

SOCIETY NEWS

Society of Military Ophthalmologists.—The newly organized Society of Military Ophthalmologists will hold a dinner on Tuesday, Oct. 16, 1951, at the Palmer House, Chicago.

Its purpose is to better acquaint ophthalmologists of the Army, Navy, and Air Force with one another. Although primarily a social gathering, the meeting will include a discussion of current military professional problems.

Eligibility for membership requires that the applicant be on active duty or retired from the military service (regular or reserve) and be certified by the American Board of Ophthalmology. Associate members include those medical officers who are eligible to the Board or who are in a training status. The society will meet annually at a dinner to be held during the annual session of the American Academy of Ophthalmology and Otolaryngology.

Members and applicants may obtain reservations for the dinner at the Academy meeting, Oct. 14, Palmer House, Chicago, from the secretary, Col. J. H. King Jr., Eye Section, Walter Reed Army Hospital, Washington, D. C.

The Purpose of the Guild

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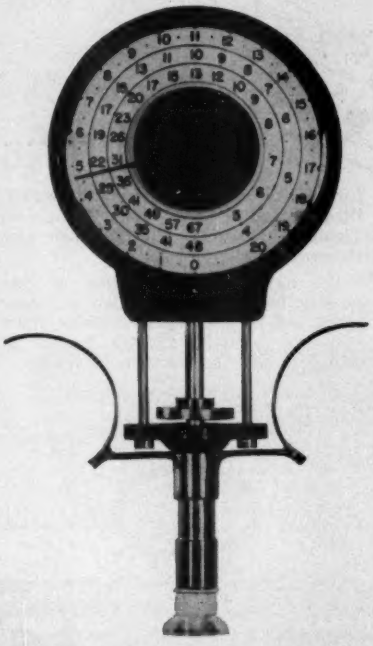

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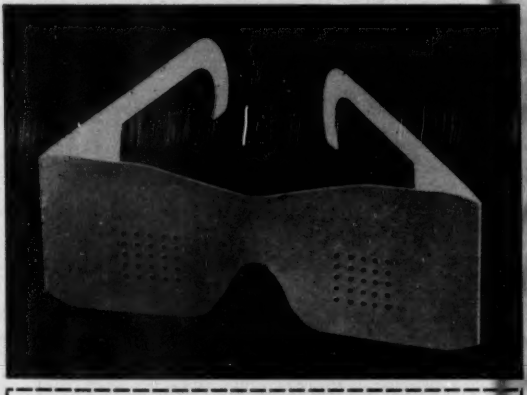

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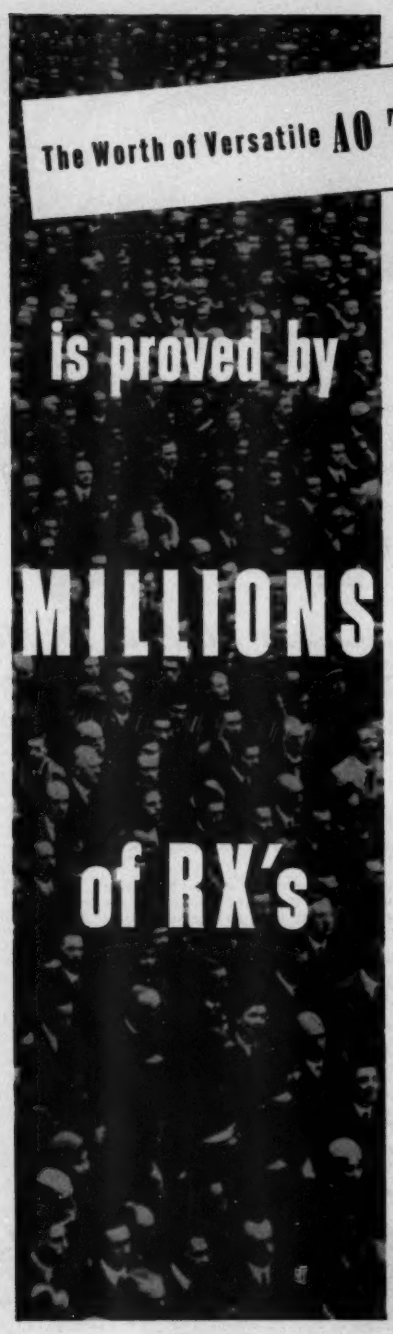

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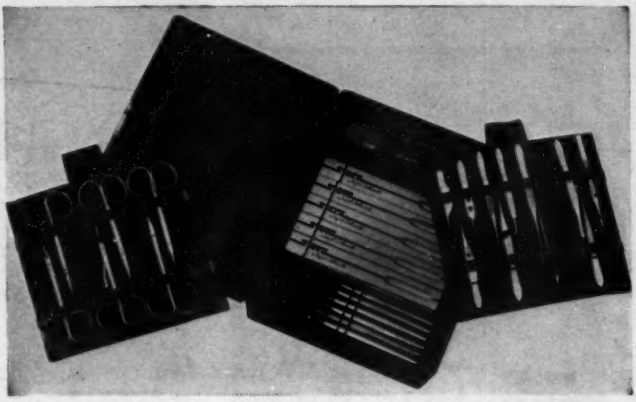

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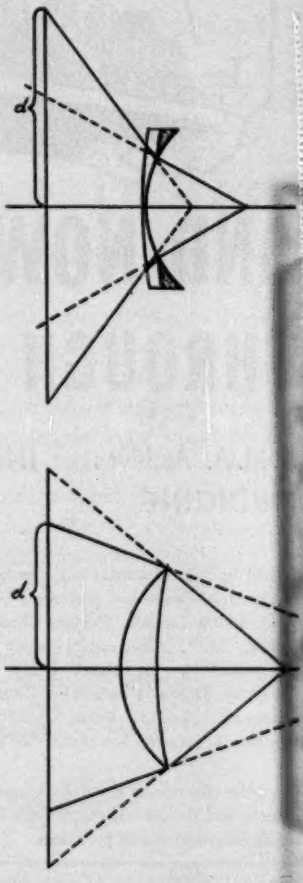

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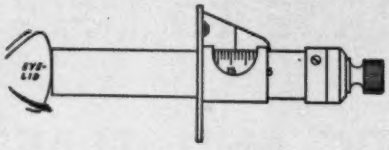

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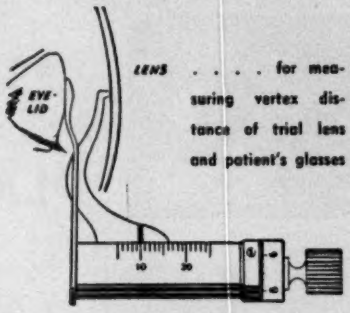

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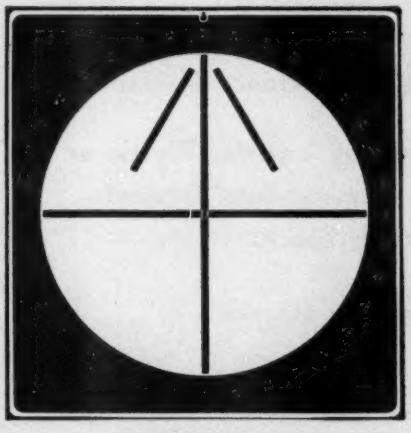

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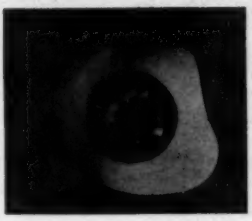

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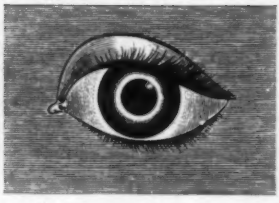

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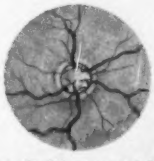

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